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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

JULY, 1926

ORIGINAL ARTICLES.

THE ETIOLOGY AND PATHOGENESIS OF ACHYLIA GASTRICA.[1]

By Knud Faber,

PROFESSOR OF MEDICINE, UNIVERSITY OF COPENHAGEN, COPENHAGEN, DENMARK.

By achylia gastrica is understood, as is well known, the very common morbid condition in which the stomach has lost its power to secrete gastric juice and especially acid gastric juice. The name, which was introduced by the American, Einhorn, in 1892, was given by him the special meaning that it was a lack of secretion which was not due to any atrophy of the gastric mucous membrane, but depended on certain nervous disturbances, therefore a *functional* and not an *organic* anomaly.[2] The phenomenon itself, the failure of the secretion, was previously known, as far back as Kussmaul and von Velden's time. It was first observed as a sign of cancer of the stomach and afterward also apart from this lesion, and in such cases it was interpreted as the result of atrophy of the mucous membrane, especially its glands, and as a sign of anadeny, that is the complete absence of glands. This was maintained particularly by Ewald and other German investigators, and it was claimed that this anadeny had been demonstrated anatomically. Einhorn, however, said that he had shown the presence of well-preserved gastric glands in cases of chronic achylia and that he had also seen chronic

[1] The Nathan Lewis Hatfield Lecture of the College of Physicians of Philadelphia, February 12, 1926.

[2] It should be pointed out that achylia, strictly speaking, refers to an absence of gastric ferments as well as hydrochloric acid; but is here used, as is the general custom, to indicate absence of hydrochloric acid. With correct examination a trace of pepsin is very often found.

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achylia cease after a certain time, in one case after some years, which was incompatible with the idea of anadeny.

While investigators were divided between these two views Martius proposed a third. He believed that Einhorn was right in holding that the achylia was functional and occurred without atrophy. But he explained it not as a result of nervous disturbances but as a congenital anomaly, a constitutional weakness of the organ which could be hereditary and a family trait like other constitutional diseases. He called this form achylia gastrica simplex or constitutional achylia.

Against these three different views, and especially in opposition to Martius' conception, I have maintained:

I. That chronic achylia has an exogenous cause and is produced by external factors acting on the stomach either by direct irritation of the mucous membrane or through the blood circulation by a toxic action on the gastric parenchyma.

II. That the anatomical picture of gastritis will develop in both cases, and that the gastritis can lead to more or less atrophy of the glands; but that achylia occurs at such an early stage of the gastritis that there is no question of atrophy, to say nothing of anadeny. That achylia therefore may be found in combination with anatomically preserved glands and undamaged gland cells, although there is a well-pronounced gastritis.

III. That in gastritis we ought not to picture a superficial catarrhal inflammation, a stomach catarrh; but a disease of the glandular parenchyma in analogy with nephritis or hepatitis.

On inquiring what arguments can be advanced for and against these four different conceptions of the pathogenesis of achylia, and more especially what there is in favor of the interpretation of chronic achylia as the result of exogenous gastritis, we find that there are three lines of investigation to be probed: (1) Clinical experiences; (2) anatomical examinations; (3) experimental investigations.

Beginning with clinical investigations, there is first of all a phenomenon which formerly was considered very important, namely, that achylia is very often entirely symptomless, and is a chance finding when a large number of persons are examined. This was thought to be incompatible with the idea of a gastritis and a proof of a functional or constitutional origin. But it is easy to show that this argument carries little weight, because the best recognized exogenous achylia, alcoholic gastritis, especially in the later stages is very commonly quite free from symptoms, and the same applies to the achylia in phthisis and other undoubted exogenous forms. Moreover this lack of symptoms is only temporary in most cases; a careful examination will usually sooner or later disclose symptoms in the digestive organs.

A greater help in understanding the question can be obtained from an investigation into the etiology of the achylia. When one

thinks of the extraordinary frequency with which achylia is encountered when a systematic examination of a large number of patients is made, one cannot but marvel how comparatively seldom it is that a definite etiology can be made out. The reason must be first, that we are still in doubt as to what causal factors should be looked for, but second that, when achylia is once established and has lasted a certain time, it will persist for the rest of the patient's life in a large number of cases. When one has to deal with a patient suffering from chronic achylia, therefore, one often has to go back to a much earlier period of the patient's life, perhaps back to the years of childhood, to find the cause of the disease. It is never possible to gauge the duration of the achylia from the length of time that the symptoms have been present, as it is so often entirely without symptoms.

The tendency of achylia to persist when once it is established makes it more common with increasing years. Thus Seidelin in Copenhagen, found absent or greatly diminished secretion in 40 per cent of the working class above the age of fifty years. In old persons of sixty-seven to ninety-two years of age Seidelin in Oslo, found anacidity, in 67 per cent.

It is consequently much more important to study the occurrence of achylia in *childhood;* it will probably be most easy to detect its cause then. It is also important for another reason. In support of the view that achylia is a constitutional disease it has been said that even in small children achylia could be demonstrated, and this was taken as proof that it was congenital. A careful study of the gastric secretion, especially the achylia of infants, has been made by different Danish clinicians (Meyer, Jacobsen, Hertz, Andersen and particularly by Chiewitz and others in C. E. Bloch's pediatric clinic in Copenhagen). In later years similar investigations have been undertaken in clinics elsewhere—especially in America, for example by Marriott in St. Louis, in New Haven, and so forth. By investigations of the gastric secretion in small children it has been found that it is best to avoid milk as a test on account of its large content of "buffer substances," especially phosphates and calcium caseinate, and this applies particularly to cow's milk. Meyer's test meal of barley water, which is most satisfactory, has proved that achylia can fairly often be demonstrated in small children, but that very obvious causes can usually be detected to account for it, and that it is most often transitory. Chiewitz and Andersen found in 127 children nothing which could be regarded as congenital achylia, and a number of other investigators have come to the same conclusion. The causes of achylia which can be detected in young children are chiefly two—parenteral febrile diseases and affections of the gastrointestinal canal, particularly the varieties of infectious enteritis.

The various febrile diseases affect the gastric secretion in small children by diminishing the production of acid. This appears not

only during the febrile stage itself, under the influence of the increased temperature, but as hypochylia or achylia occurring in convalescence and often lasting a long time. Hertz, Chiewitz and Andersen observed this, for instance, after influenza, angina, pneumonia, bronchitis and similar complaints. In some cases a normal acid secretion was demonstrated in the children before the acute disease started and after it was over there was an achylia of long duration.

Far more commonly, however, was achylia detected in small children with gastroenteritis. The stomach seems indeed to be influenced very easily by infectious enteritis and chronic achylia is often found in such children. It may disappear in company with the intestinal disturbance; or may persist for a long while. It may be attended by anemia and marasmus, or it may occur alone. In 33 out of 64 small children with chronic gastrointestinal dyspepsia and atrophy, C. E. Bloch found a diminished secretion of acid at the climax of the disease. In 18 cases the secretion rapidly returned to normal at the same time that a general improvement took place but in 15 cases there was complete achylia lasting for weeks or months, observed up to eleven months. In some of these also it could be shown that the secretion became normal again; in other cases the achylia seemed to be lasting and associated with profound damage to the secretory apparatus.

In opposition to the theory that the achylia is congenital, we find, then, well-marked exogenous achylia and obvious causative factors. The latter chiefly consist of acute infections, especially of the intestinal canal. It is important to note that achylia in children is often a temporary phenomenon, more frequently than in adults, but that, on the other hand, it may last a very long time. In certain cases it seems to last years without hindering the nutrition and fairly normal development of the child.

Passing on now to *adults*, we observe quite analogous conditions, and there is cause to dwell particularly on the cases of achylia in the different groups where an exogenous origin can definitely be detected.

A very obvious cause is the direct damage and irritation of the mucous membrane of the stomach from taking alcohol. Vogelius has investigated a large number of patients in Copenhagen with chronic alcoholism. He could demonstrate achylia in 50 to 60 per cent. What is of special interest here is that he could show that some of the patients who came into the hospital with signs of recrudescence of the gastritis, namely, with severe dyspeptic symptoms, vomiting and so forth, had achylia; but that it disappeared fairly rapidly when the patient abstained from alcohol and was on a light diet. Not before these bouts had been repeated several times did the achylia become constant. The lesion of the gastric mucous membrane had increased and the failure of the secretion was permanent.

In contrast to this direct action on the mucous membrane, there is the change which occurs during a *general intoxication* of the organism and above all in acute infections. Just as in children, it is especially the intestinal infections which affect the stomach, as for instance, typhoid fever, paratyphoid fever and dysentery. Achylia is very commonly found after these diseases particularly the last, and just as in the case of children, it may disappear again in the course of some weeks or months. In a certain number of cases, however, the achylia remains, presumably for the rest of the patient's life. We see the same thing in chronic infections, especially tuberculosis. In phthisis Permin has demonstrated achylia in 34 per cent in the early stages, and even in 75 per cent in the final stage of the disease. An intoxication is the most natural explanation. Guido has recently discovered achylia in 26 per cent of malaria cases, and in some cases the achylia has been constant. In syphilis, achylia also is common. Apparently, widely different infectious diseases are able to influence the gastric secretion in a similar manner.

But it is not only the intoxication produced by infectious diseases that can give rise to achylia. We have a striking example in Graves' disease, where it is very common and occurs in 50 per cent of the patients. In this case it is also a question of an intoxication of the organism, but it is an autointoxication not caused by microbes.

The same applies to the achylia so frequently seen during pregnancy, especially in those cases of the intoxication of pregnancy which lead to eclampsia and similar serious conditions.

In Denmark, Kramer Petersen has shown that a diminished gastric secretion occurs in a great number of pregnant women, (in 86 per cent) the last few months before labor and that an achylia is very common at this time. In patients with eclampsia, it can be demonstrated in 43 per cent of the cases.

We see, therefore, that the gastric mucous membrane and its secretory apparatus behave in a manner similar to that of other parenchymatous organs, especially the kidneys and liver, and that it is affected by infections and by intoxications. We must call these causes exogenous, and they are observed so frequently and are of such different kinds that they can fully explain the many cases where the cause of the achylia cannot be detected directly.

One of Einhorn's main arguments in favor of achylia in many cases being necessarily of functional origin was that the achylia might occur for a time and then subside. Such transient achylia is certainly inconsistent with the idea of a total atrophy of the mucous membrane, but it was wrongly interpreted as an argument against there being any inflammation whatever and as evidence against an exogenous origin for the achylia.

We have, however, in cases of alcoholic gastritis seen that the very common phenomenon occurs that achylia only remains for a

time and then disappears when the abuse of alcohol is prevented, again to make an appearance when an exacerbation of the gastritis sets in. Likewise we have observed it to be very common in infants, that when their gastric secretion was reduced or suspended on account of some toxic influence, the secretion recurred after a longer or shorter period. It would appear as if the gastric secretion were much more easily influenced in children than in adults, is subsiding more easily and reappearing more quickly. In adults it is, however, a fairly frequent phenomenon that achylia may also disappear without it being possible for us to demonstrate such a direct irritant as alcohol. Patients with achylia come for treatment, but gradually as their condition improves by means of dieting and rest, the secretion recommences and after a period of hypoachylia we find normal figures at our examinations. Naturally this is especially observed in cases of what might be termed pseudoachylia, where by fractional examination a small and retarded secretion can be demonstrated, but it is also complete anacidity. The explanation of the fact that an achylia subsides and secretion returns is naturally to be sought in the improvement in the gastritis. In any case it may not be utilized as an argument against the existence of a gastritis. The younger the patients, the more frequently we note the return of the secretion; the older the patients and the longer the gastritis has persisted, the more stable is the achylia.

These conditions are further elucidated when we turn to an investigation into the *anatomical findings*. In chronic achylia we discover that it is a field which has only been thoroughly investigated comparatively recently. The investigations into the morbid anatomy of diseases of the different organs, which were so extensively carried out in the last century, usually did not deal with the stomach and intestines when it was a question of microscopic examination. The reason was principally that after death their mucous membranes are so quickly acted upon by the digestive fluids and cadaverous putrefaction. Hayem in France was the first to attempt to combat this by fixation directly after death. In conjunction with C. E. Bloch in 1899 I introduced the injection of a 10 per cent formalin solution (*i. e.*, 4 per cent formaldehyde) into the abdomen immediately after death. We thus obtained excellently fixed stomachs and could subject them to a thorough anatomical examination. I will show you a series of pictures of the changes seen in the gastric mucous membrane in chronic achylia. In many of the patients the digestive disturbances gave rise to extremely few symptoms or none whatever, and the cause of the disease was unknown. The material thus comprises those cases which from the clinical picture one would be inclined to regard as constitutional or nervous achylia, as cases of *achylia simplex*.

The first difficulty was to find really normal stomachs. It is not sufficient that there has been no morbid symptoms and that the

secretion was normal. As in all other organs there is no absolute parallelism between anatomical lesion and disturbance of physiologic function and a normal secretion may well be associated with anatomical signs of inflammation.

The first picture shows an absolutely sound stomach in a child who died from meningitis (Fig. 1). The glands are observed to be placed close together and there is no trace of interstitial inflammation, no round cells between the gland tubules. In the following pictures, on the other hand, we see inflammatory processes throughout the mucous membrane (Figs. 2 and 3). The latter, however, may be so well preserved at first that the glandular layer is practically uninjured.

In some cases the inflammatory phenomena are very strongly marked, but in others, where the achylia has only existed for a short period, only slight changes are observed. As an example, Fig. 4 shows the stomach from a child aged one and a half years. After being quite healthy for one year it got an acute attack of enteritis, followed by achylia ascertained to have existed for six months, as the child died from other causes. The mucous membrane was well preserved, but a slight infiltration of round cells is observed. It is obvious that in this case the intoxication has directly affected the secretory apparatus and caused beginning anatomic changes.

Gradually as the inflammation develops signs of lesion of the glands put in an appearance. They get fewer in numbers, become separated from one another by the inflammation, atrophy, tend more and more to become vestiges and finally completely vanish (Figs. 5, 6, 7). We then see the stomach consisting only of granulation tissue covered merely by the surface epithelium of the stomach. There is now complete anadeny. Other changes are also observed. The accumulations of round cells resembling follicles may have developed into large typical lymphoid follicles; follicular gastritis is present (Fig. 8). Cystic formations in the necrosing glands are often seen, and cysts may sometimes be very prominent. It frequently shows the curious phenomenon that the stomach's superficial epithelium is transformed into intestinal epithelium which is specially characterized by the goblet cells containing mucus. This is never found in the normal stomach. By means of a very thorough examination of twelve normal or almost normal stomachs, Lange, in my clinic found normal gastric epithelium throughout, while in 14 stomachs in patients with achylia and gastritis, intestinal elements were discovered scattered about in 10 of them, that is, in 75 per cent. In the picture (Fig. 9) one sees Lieberkühn's glands with Paneth cells and only small rests of stomach glands. It seems as if these heterotopic formations especially occur when the gastric secretion has ceased, and the mucous membrane, therefore, practically functions as an intestinal mucous membrane.

Thus we see an even transition from the slightly affected stomachs to cases where there are severe anatomical changes with profound injury to the secretory apparatus. Not until the gastritis has persisted for a considerable time do we arrive at the atrophic stage. The examples of complete atrophy I have shown you were found in aged or middle-aged persons, where the achylia may be presumed to have existed for many years. It is easily comprehended that there is achylia in these cases; it has, on the contrary, in agreement with Einhorn been emphasized that when the glands in the milder cases were well preserved, then the local affection of the mucous membrane could not be the cause of achylia. As already mentioned the anatomical changes are but the signs of the disease visible to us.

An intoxication may influence the cells and their innervation apparatus immediately, even before anatomical changes have manifested themselves, and even in pronounced anatomical inflammatory phenomena the secretory cells may appear to be quite natural at the first anatomical examination. The accompanying Figure 10 is taken from a patient suffering from cancer of the stomach, who had showed symptoms for half a year before operation and who had a complete anacidity. By Altmann's stain we observe both the chief cells and especially the acid-secreting cells to be absolutely normal and prepared to resume their secretion should the harmful influence subside. The next illustration (Fig. 11) originates from another patient with cancer ventriculi and achylia. Here the cells have commenced to degenerate and presumably will no more be able to resume their function.

That achylia in cancer is neither neurogenic nor constitutional all are certainly agreed. The pictures thus show clearly that we cannot conclude from the cells being preserved in a functionally active state that it is not a question of a local affection of the stomach, of gastritis.

What now can we conclude from these anatomical investigations? We may infer that gastritis is a very common phenomenon, and that from an anatomical point of view it shows great similarity to chronic inflammation in other large glandular organs like the kidneys and liver. We find failure of the secretion as a perfectly natural result of the inflammation and atrophy of the glands, just as we find insufficiency of the organs of the kidneys and liver. We realize that we cannot look upon gastritis from the old standpoint, gastric catarrh. It is a disease of the whole gastric parenchyma, not merely of the mucous-producing top layer of the mucous membrane. We understand that gastritis can be produced both by surface irritation and by hematogenous intoxication. We understand also that gastritis may occur which does not lead to achylia, as is frequently observed to a greater or less extent in gastric ulcer.

But does this imply that all achylia is always due to gastritis? Cannot the other causes—nervous influences or congenital anom-

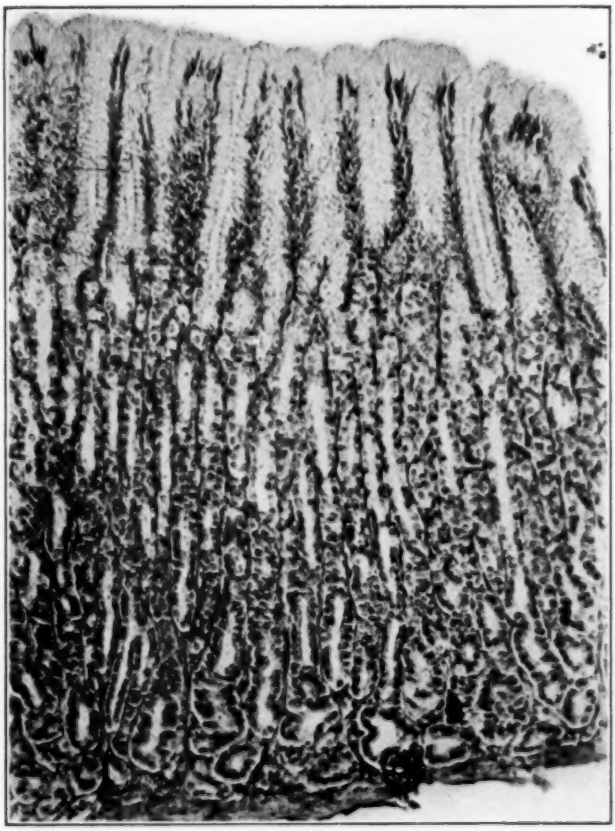

FIG. 1.—Normal mucous membrane of the stomach from child with meningitis.

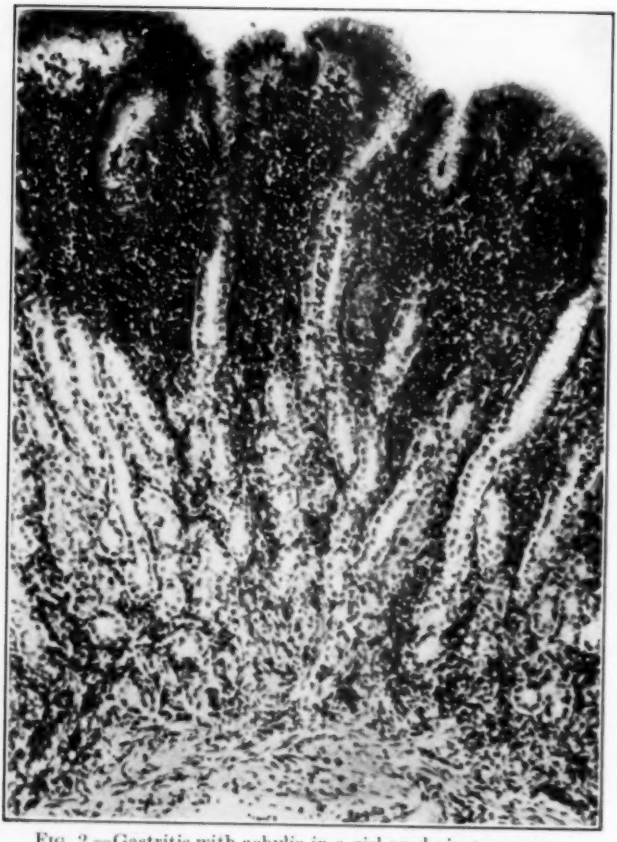

FIG. 2.—Gastritis with achylia in a girl aged nineteen years.

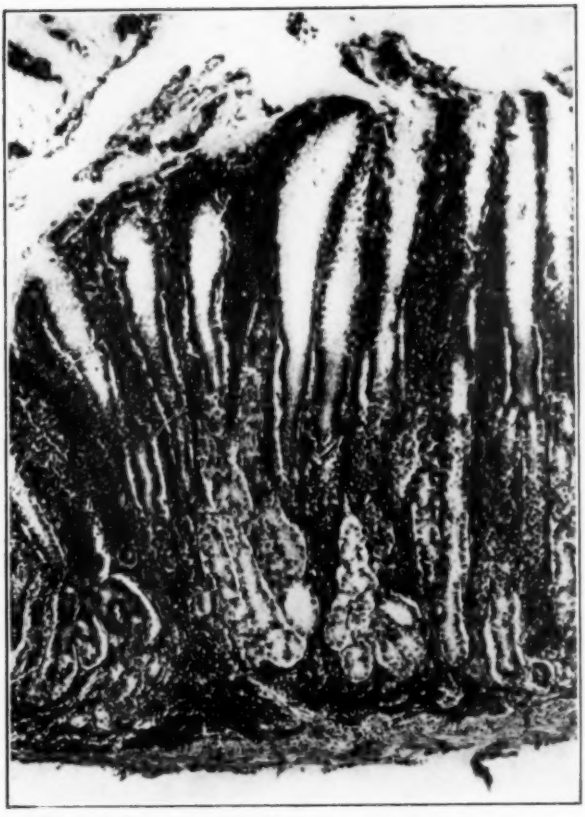

FIG. 3.—Gastritis with achylia in a man aged forty years.

FIG. 4.—Achylia in a child aged one and a half years. Commencing gastritis.

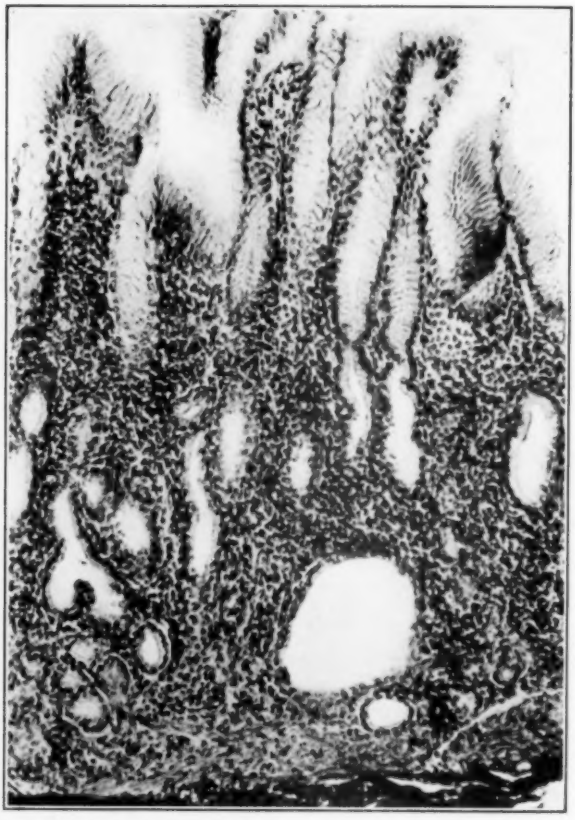

FIG. 5.—Gastritis alcoholica with achylia gastrica in a man aged fifty-one years. Commencing atrophy of the glands and some cysts.

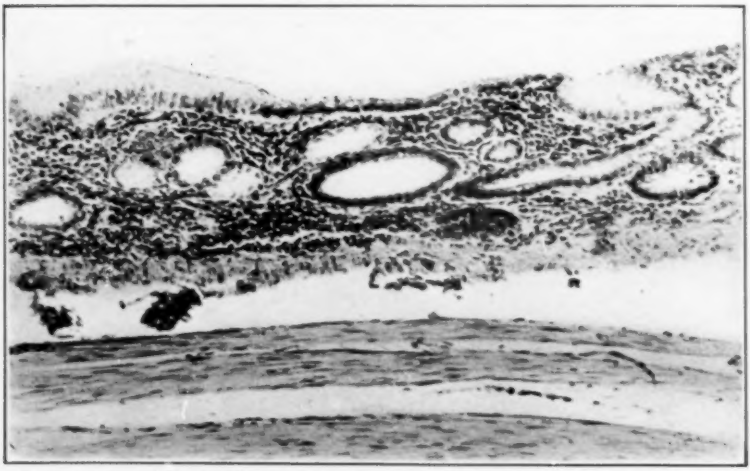

FIG. 6.—Complete atrophy of the mucous membrane of stomach. No secreting glands. From a man aged forty-two years, who had gastric symptoms for ten years.

FIG. 7.—Atrophy of the mucous membrane of the stomach; complete anadeny. Gastric epithelium replaced by intestinal epithelium with goblet cells.

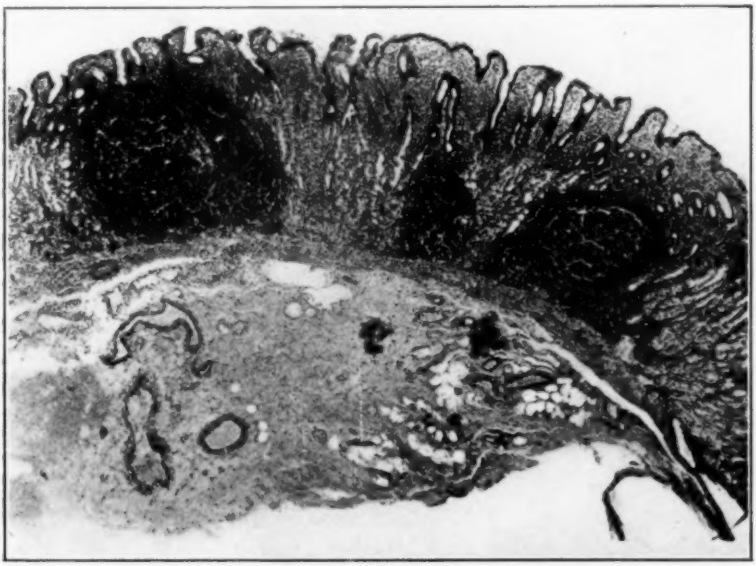

FIG. 8.—Follicular gastritis with achylia in a girl aged twenty-five years.

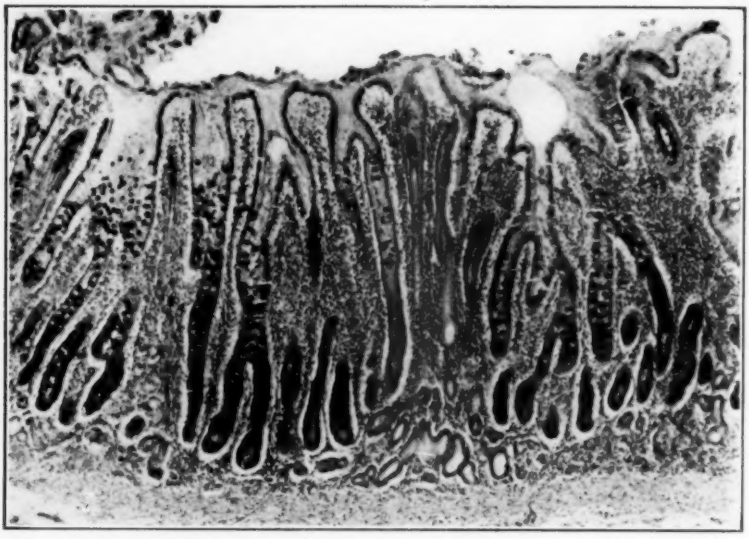

FIG. 9.—Chronic gastritis alcoholica in an old man aged fifty years. In the mucous membrane nearly all the gastric glands have disappeared and are replaced by Lieberkün's glands with Tanable cells in the bottom. The epithelium of the intestinal type with goblet cells.

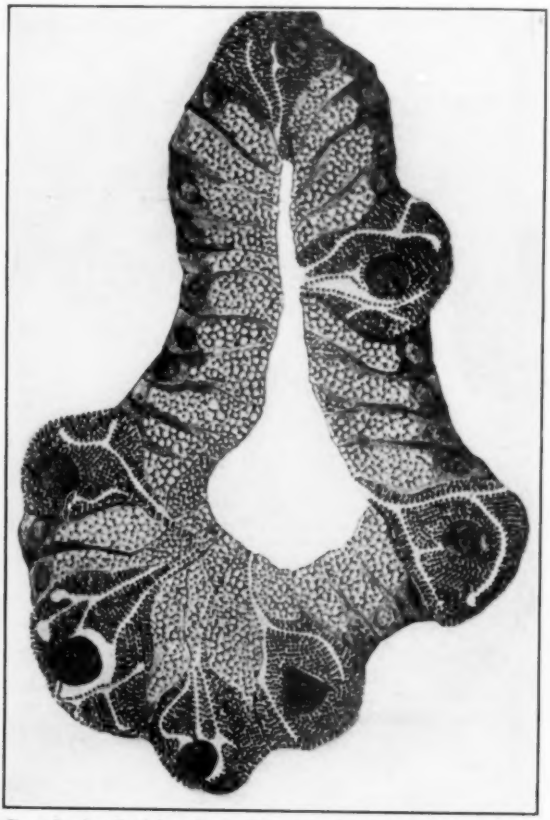

FIG. 10.—Gastric gland with well preserved acid cells in a case of stomach cancer which had given symptoms for a half year. Complete anacidity. Altmann's stain.

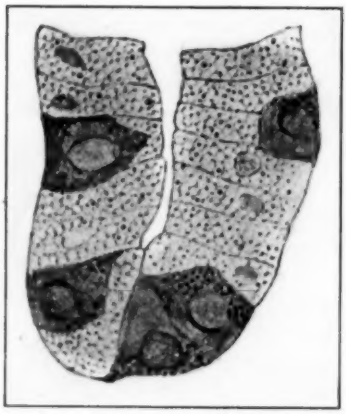

FIG. 11.—Gastric gland from a case of stomach cancer which had given symptoms for three months. Complete anacidity. The acid cells and the chief cells show degeneration. Altmann's stain.

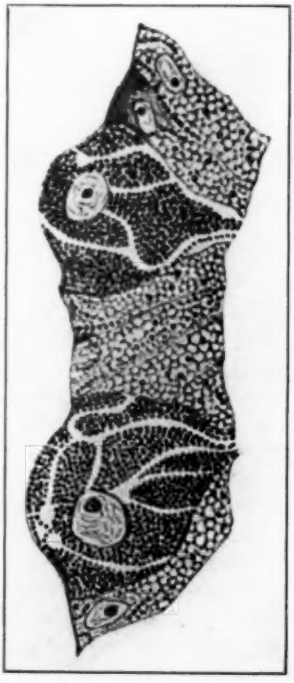

FIG. 12.—Part of gastric gland in anacidity after cutting both vagi in a dog.

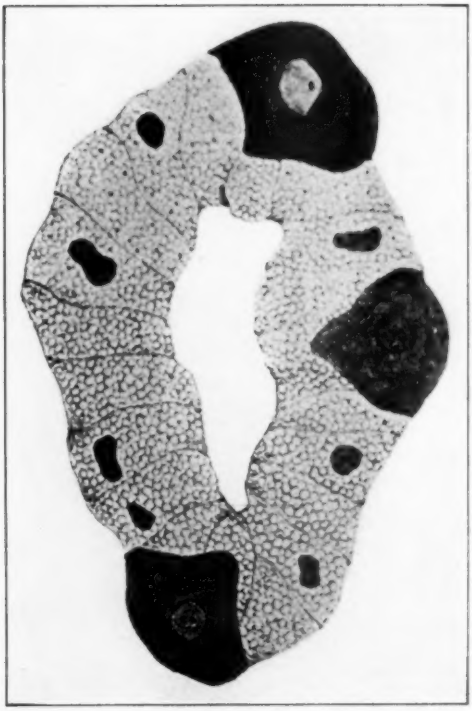

FIG. 13.—Gastric gland with degeneration of both sets of cells in gastritis after poisoning by diphtheric toxin.

alies—in some cases be the prime ones and the gastritis only a secondary effect, perhaps produced by the deficient gastric digestion. If we accept the views given here about intoxication and direct irritation being the principal causes, we need no other actual explanation; but we cannot exclude, clinically or anatomically, that at all events in some cases the pathogenesis may be different from what we have put forward.

With regard to nervous achylia, its existence can hardly be denied, especially since Bennet and Dodds have produced it experimentally by suggestion under hypnosis. Another question is whether we can get genuine chronic achylia through nervous channels or only merely a purely temporary disorder.

About these questions we can obtain important information from the third group of investigations, namely, *experiments on animals.* We know from the work of Pawlow and his pupils and from Carlson and Ivy that in the secretion of gastric juice there is a primary cephalic period governed by an influence of a cerebral nature, induced reflexly or psychically through the vagus and a second humoral phase governed by chemical agencies from the blood. Not only a secretion but also an inhibition can in the first phase be produced through the nerve. After complete division of the vagi the secretion is observed to decrease markedly or entirely cease for a while. But this phase proves to be temporary, the secretion returning after some time has elapsed. Even if the stomach is completely isolated from all its innervation, both sympathetic and parasympathetic, it yields a fairly abundant secretion after the introduction of food. The second phase can only be inhibited temporarily th ough nervous channels.

In accordance with this we do not see permanent but only temporary achylia of nervous origin. It is found moreover, when the gland cells are examined histologically, that in spite of the temporary failure of the secretion, they preserve their appearance as in actively secreting glands. They are ready to resume their work at any time whatever, just as we have seen it in the beginning gastritis.

I can illustrate this with pictures for which I am indebted to an interesting work by Einar Thomsen carried out in the Physiological Institute in Copenhagen. In dogs with a gastric fistula, he was able to confirm that an achylia could be the result of cutting both vagi and that the completely nerveless stomach was still capable of secreting. Only transient achylia could be provoked through nervous paths, and the anatomical examination of the secreting cells showed normal appearance (Fig. 12). On the other hand, he could produce a true chronic achylia experimentally by the other methods we arrived at from a consideration of the clinical factors, namely, by direct irritation of the mucous membrane, or through the blood, by bacterial intoxication. Gastritis was caused by the administration of alcohol which first manifested itself by transient hypersecre-

tion and then by more or less complete achylia. Anatomically there were signs of gastritis with interstitial changes as in man, but the gland cells ceased to secrete long before they began to degenerate.

For bacterial toxin he used chiefly diphtheria toxin. By the intravenous injection of this poison a very pronounced acute gastritis with great hyperemia and interstitial changes were produced just as we saw in the picture I have shown of human gastritis. The secretion ceased and here he could rather soon see the degeneration of the glandular cells (Fig. 13).

Thomsen could also produce a pure toxic diminution of the gastric secretion by feeding his dogs with thyroid extract. The gastric secretion nearly ceased but no real achylia was produced and the secretion returned when the thyroid intoxication was stopped. In this case there was no sign of gastritis, during the experiment.

These experimental researches thus prove to us that we may sometimes see a passing achylia of nervous origin, but that a chronic achylia arises either by direct injury to the stomach or by hematogenic intoxication. This agrees with the clinical and anatomical studies.

It remains to say a few words about the theory advanced especially by Martius of the constitutional achylia, the achylia gastrica simplex. He believed it was due to a congenital weakness, and that it was a true constitutional disease. There is no doubt that he came to that conclusion because achylia was so common and so often symptomless. I have shown that these arguments are without value. But an attempt has been made to support the hypothesis: (1) By showing that achylia can occur in children, in fact, even in small children, and (2) by exploiting the fact that it may occur as a family disease which attacks several members of the same family.

I have already made clear the situation with regard to the children and have shown that no argument is forthcoming from this quarter in favor of the theory of congenital achylia. It would be of greater value if the occurrence in families could be demonstrated on a larger scale. It would be necessary, however, to be rather cautious, as achylia is so extremely common a disease. Large and convincing series of cases in families I have not yet come across. The frequent occurrence of achylia among brothers and sisters or relatives would not in itself put an exogenous origin out of court, for example, an intoxication by infection. It would at most show a greater family susceptibility to external influences, which must be distinguished from a genuine congenital hereditary disease, as, for example, Huntington's chorea.

Summary.—We have arrived at the result, then, that the very common and very important disease which we usually call achylia gastrica has nothing particularly remarkable in its etiology and pathogenesis which marks it out from the diseases of other organs.

It is due to disease of the gastric mucous membrane with its extensive glandular apparatus. When it is excited through nervous channels, it can only persist for a short time but apart from this it is due to the same causes which we know produce disease in other organs—direct irritation or hematogenous intoxication by bacterial toxins or autotoxins. With the exception, perhaps, of the initial stage of intoxication, the natural term for the disease is gastritis, by which is to be understood, not the old conception gastric catarrh, but a disease of the glandular parenchyma of an inflammatory nature.

The reason that the anatomical side of the question has come under consideration much later in this case than in that of other glandular organs like the kidneys and liver, is because postmortem changes take place so rapidly. As soon as one has learned how to avoid these, the analogy is obvious and gastritis takes its natural place by the side of nephritis and hepatitis.

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PHYSIOLOGY OF THE MELTZER-LYON TEST.

By M. Chiray,

professeur agrégé, faculté de médecine, paris, médécin des hôpitaux,

and

I. Pavel,

prosector, coltza hospital, and assistant, faculté de médecine, bucharest.

The Meltzer-Lyon test, which has received so much attention and study during the last few years and which has caused some revision of clinical ideas concerning gall-bladder pathology, has raised various problems, of which a certain number have not been solved to perfect satisfaction. Of these problems, the one concerning the physiology of the test is most difficult. It is by no means easy to determine the mechanism producing discharge of "bile B" after the instillation of a 33 per cent solution of magnesium sulphate

into the duodenum. Various authors have advanced various explanations of the discharge.

First, the physiologic studies originating the test suggested that the latter might be explained by the law of contrary innervation. This theory has been brilliantly defended by Meltzer. However, the American physiologist, when he formulated this law, had not yet considered the test in question, which indeed had not yet been devised when Meltzer first suggested the idea of introducing, through the duodenal catheter, a solution of magnesium sulphate, to release small calculi retained above the sphincter of Oddi. Clinical applications of the method have not been successful in the way originally intended, but have supplied other results which have proved much more interesting. The influence of chance in scientific research has been strikingly illustrated in this development. It is true that one author (Allard) has claimed to have released biliary calculi by injecting into the duodenum very large quantities of magnesium sulphate. This method, however, seems to us not wholly above criticism.

Utilizing the original Meltzer procedure, Lyon was able to obtain the dark-colored bile which he considered to represent the bile of the gall bladder. Later studies have confirmed his opinion, for operations and autopsies have clearly shown, during recent years, that bile collected by the Meltzer-Lyon method is practically identical with that obtained directly from the gall bladder. The authors contributing to the question include Friedenwald, Martindale and Kearney, Whipple, Hollander, Stepp, Lepehne, Deloch, Chiray, Lebon and Milochevitch, Rathery, Labbé, de Moor and Nepveux, Winkelstein, Simici.

Experimental studies have proved more contradictory. While those made by Stepp and Duttmann have been confirmatory, others have seemed to show that the two biles are not identical. Many of the tests, however, may be sharply criticised. We have recently shown some of the causes of errors incurred.

The problem of the physiologic mechanism governing the excretion of bile from the gall bladder after stimulating the duodenum with magnesium sulphate must be attacked. Lyon thinks that the excretion is referable to the law of contrary innervation, and that injection of the solution simultaneously opens the sphincter of Oddi and causes contraction of the gall bladder, saying, "the inference was plain that if this law of contrary innervation was sound, anything which would cause inhibition in the tonus of Oddi's sphincter must, *ipso facto*, cause contraction of the gall bladder musculature." Lyon therefore exceeds Meltzer's original view and his theory even extends beyond the scope of the law of contrary innervation. The lack of accord has been recently explained, Meltzer's opinion being shown through a correspondence between the two investigators, published by Lyon. So it is remarked that

"the law of contrary innervation applies only to the functions of organs of living animals, it does not apply to inorganic substances. It does not mean, for instance, that magnesium salts which cause a relaxation of one component of an organ must, *ipso facto*, cause a contraction of an antagonistic component in the same organ, or that barium salts, which, as a rule, cause contraction of one component, cause inhibition of the antagonistic component." It may be also observed here that the law of contrary innervation applies to normal conditions in physiology. That is to say, admitting that contraction of the gall bladder be followed by relaxation of Oddi's sphincter, it does not necessarily follow that the relaxation of the sphincter will produce the contraction of the gall bladder normally preceding relaxation. (The law of contrary innervation should be interpreted physiologically. It is not necessary to assign the vagus to the gall bladder and the sympathetic to the sphincter of Oddi, as may be readily ascertained by referring to the work of Bayliss and Starling on intestinal contraction, which is governed by a law included under the general one of contrary innervation. Local irritation of any part of the intestine produces contraction above the point irritated and inhibition of the portion immediately below, in spite of the identical innervation of the upper and lower portions.)

The work of Meltzer and Lyon has given rise both to critical examination of the law of contrary innervation and to the many clinical and experimental studies by Crohn, Reiss and Radin, Bassler, Luckett and Lutz, Diamond, Winkelstein, Harer, Harjis and von Metter. Some of these studies have seemed to show that the gall bladder has no contractility whatever. This idea would completely nullify ideas considered classic since the work of Doyon. Under such conditions, another interpretation would assign to the Oddi sphincter a dominant influence in the mechanism of induced gall-bladder excretion. Partisans of this interpretation consider that the application of magnesium sulphate to the duodenal mucosa causes relaxation of the Oddi sphincter, followed by emptying of the gall bladder of its bile by pressure which some consider external, others internal.

This hypothesis is readily disproved. Bile by no means escapes from the gall bladder whenever the Oddi sphincter is open. All who employ duodenal intubation know that the presence of the catheter within the duodenum causes the sphincter to open and that bile then flows from the common duct, while bile never flows, at least under ordinary conditions, from the gall bladder, either accompanying or following intubation. If the sphincter is open in the absence of duodenal irritation produced by magnesium sulphate, bile does not escape from the gall bladder. This fact indicates that the sphincter of Oddi may have nothing to do with evacuation of the gall bladder following injection into the duodenum of magnesium

sulphate. If it plays any part at all here, it acts merely as an obstacle to the flow of "bile B." This condition occurs in certain pathologic states, as in pyloroduodenal ulcer. Only one probable cause of gall-bladder excretion thus exists. It consists of the initiation of gall-bladder contraction by any sort of duodenal irritation, including irritation by magnesium sulphate. It is not neces-

FIG. 1.—Reduced by one-third. Slow contraction of the gall bladder of the type described by Doyon.

sary to discuss the theory that the gall bladder is emptied by pressure of near-by organs, especially the diaphragm. Such a theory does not explain satisfactorily the normal phenomena.

Our clinical and experimental observation has led us to believe that the physiologic cause determining evacuation of "bile B" consists in contractions of the muscular tunic of the gall bladder. To render this theory substantial, we have been obliged to prove that the gall bladder is thus really contractile. Patient studies made *in vitro* with canine gall bladders have convinced us that

contractility of the gall bladder not only exists, but that it suffices to perform the task which may be reasonably assigned to it, namely, evacuation of the gall bladder. For details of our technique and for our results, the reader may refer to our paper on the subject. Here we shall merely give a rapid review of certain facts essential for understanding the contractility of the gall bladder. These facts support our conception of the mechanism of the Meltzer-Lyon test.

Our tracings convey an exact and complete idea of spontaneous contractions in the gall bladder. The contractions are of two types. The first type, occurring in all the tracings, develops slowly in a period ranging from thirty minutes to two hours (Fig. 1). The second type presents small and frequent contractions (2 to 3 per minute) which are difficult to elicit. Both types may exist in the same tracing (Fig. 2). Contraction of the gall bladder is not mythical, but its amplitude is small and its speed very slow. These characteristics appear very clearly if the contraction of the gall bladder be compared with that of the intestine. Intestinal contractions are visible to the naked eye, which is rarely true of gall bladder contractions. The amplitude and rapidity of intestinal contraction are so much greater than those of the gall bladder that it may be questioned whether the muscular tunic of the gall bladder can really expel the bile contained within the latter. Some authors, while recognizing the existence of the gall bladder contractions, have doubted their ability to evacuate the bile.

We are far from sharing this opinion. Besides, we can show that there is a very easy explanation of the difference, noted above, between the intestinal and the gall bladder contractility. The function devolving upon the intestinal wall demands contractile force quite different from that necessary in the gall bladder. Contractions required to propel an enormous quantity of alimentary material along the bowel, in a relatively short time, and to impel onward a paste becoming thicker and denser as the last intestinal loops are approached, and as absorption becomes complete, must have a force which may be readily imagined. The effort made by the gall bladder is slight, for its liquid content, though sometimes concentrated, is much less so than the intestinal content. Evacuation of the bile anatomically demands a muscular wall, and physiologically requires contractile force, much less powerful than those of the intestine. The physiology of the gall bladder also differs from that of the intestine because of the fact that the former is not a continuous tube with a double opening, but a closed pouch with but one outlet. Under such conditions, the feeblest contraction, and one much less powerful than intestinal contractility, becomes active, effective and capable of evacuating the bile through the sole existing outlet. Contractions of the gall bladder are still more

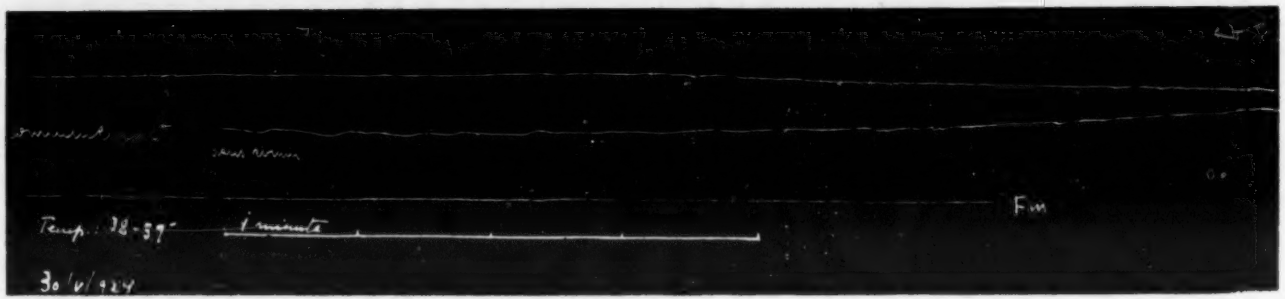

FIG. 2.—Reduced by one-third. Complete spontaneous contractions of the gall bladder. The curve begins on the middle tracing and shows the small contractions, occurring two to three per minute, which disappear as the slow tonic contraction develops. The tracing is continued in the upper line, which shows how the slow contraction still continues after thirty minutes and then begins to decline, near its middle portion. Termination of the slow contraction, occurring in sixty-six minutes, is shown in the lowest line.

promoted by the anatomic arrangement of its muscular fibers. The latter have been studied histologically in various animal species by Ranvier and Doyon. These studies in comparative anatomy have contributed the important information that the musculature of the gall bladder is reticular. In man, where such studies are not fully complete, circular fibers seem to predominate (Hendrickson, Schikinami). A reticular arrangement favors contraction in all diameters, and even constitutes "the most perfect system from the viewpoint of constricting contractions" (Ranvier).

Such contraction, and the difficulty of observing it with the naked eye, are easily shown experimentally. This difficulty explains why so many investigators have denied that the gall bladder possesses contractility. The "small and frequent contractions" mentioned above are so small, in fact, that they are hardly perceptible. This fact is readily understood. But the larger and slower contractions, also mentioned, should seemingly be perceptible and at first it is not easy to see why they are also difficult to note. We are inclined to believe that it is because a contraction in the long axis of the gall bladder occurs at the moment when the generalized contractions occur. The transverse and longitudinal diameters are thus both retracted together, and the transverse diameter does not diminish by itself alone. If it did so, the contractions would be more easily perceived, but as it is they are masked. Iwao Matsuo, whose studies in man on obtaining "bile B" by means of magnesium sulphate were made at the same time as our own investigations, has not only observed the gall-bladder contractions, but has tested them by measuring the diameters of the gall bladder.

In vitro, the contractility of the gall bladder may be enhanced by different methods of stimulation. Temperatures ranging from 46° to 48° have produced in our hands contractions whose acuity and amplitude are very marked. Doyon obtained similar results with the electric current in dogs, and Ditrich, Gerlach and Hertz confirmed Doyon's results by working with the gall bladder of an executed criminal.

However, the contractions which are most interesting, because they may be induced in the living human subject, are those following peripheral stimulation of the vegetative nervous system with eserin or pilocarpin. These substances much increase the acuity and duration of the larger contraction mentioned, which usually develops very slowly (Fig. 3). Pilocarpin may produce wholly unusual contractions of the gall bladder, as compared with the contractions usually occurring in it (Fig. 4).

These various manifestations of the contractility of the gall bladder show beyond reasonable doubt that the flow of "bile B" after introducing magnesium sulphate into the duodenum is due to contractions of the gall bladder. In cases of stasis, the bile within the gall bladder may doubtless appear as soon as the sphincter

opens, and before magnesium sulphate is introduced into the duodenum. Such cases, however, are almost or practically pathologic,

FIG. 3.—Reduced by one-half. Action of pilocarpin on gall bladder contractility. Atropin also shown. The substances are mixed *in vitro* with 150 cc. normal saline solution. The contraction produced is prompter and more prolonged. The original level of the tracing is recovered only after one hundred minutes.

and do not explain the physiology of the Meltzer-Lyon test in the normal individual.

The mechanism by which magnesium sulphate produces contractions of the gall bladder merits some comment. Some have

considered it due to reflex, others to humoral, influences. Everything seems to indicate that the effect is due to a reflex, or rather to a series of interrelated reflexes. It is analogous to the general intestinal peristalsis caused by saline purgative enemata. This analogy has been shown by Hans Simon, of Berlin. Meltzer, who similarly examined the question, considered the effect a humoral

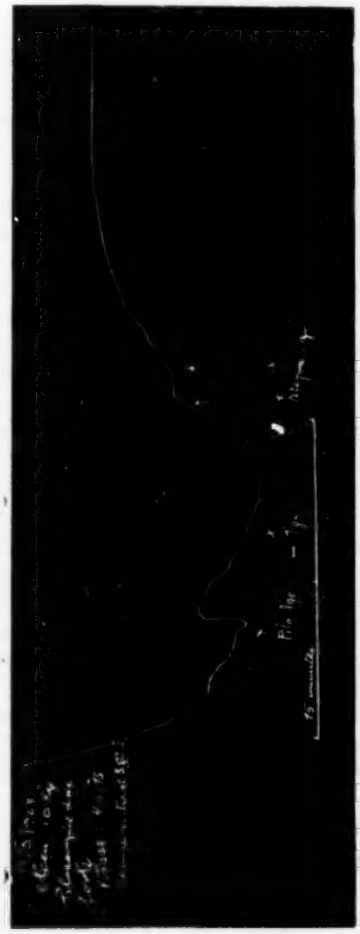

FIG. 4.—Reduced by one-half. Action of large doses of pilocarpin on gall-bladder contractility. A single application of the substance produces an abrupt and marked contraction. The curve falls to its original level in eight to ten minutes, a tonic contraction then developing which continues for more than three hours. Atropin has no effect upon this tonic contraction.

one, advancing the idea that magnesium sulphate and the sodium chlorid of the chyme react to produce sodium sulphate, the latter acting through the blood upon the nervous centers governing the musculature of the gall bladder.

Instead of Meltzer's theory, we prefer the motor reflex hypothesis. It must be pointed out that many substances other than magnesium

sulphate may produce the same reflex effect. Among such substances are acidulated or simple hot water, a solution of Witte's peptone (the Stepp method), and olive oil. Meltzer's theory, referring to magnesium sulphate, can scarcely be extended to all these other substances.

The reason why magnesium sulphate when taken by mouth acts differently from its behavior when introduced by the duodenal tube also merits discussion. Opinion on the question has varied. Our experience indicates that a real difference does exist. We are inclined to think that the effect produced by magnesium sulphate in the Meltzer-Lyon test is due to the greater and more vigorous contact of magnesium sulphate with the duodenal mucosa permitted by introduction directly into the duodenum. When taken orally, the salt is retained by the stomach to some extent and may become altered there. It is at least diluted, and escapes through the pylorus only in successive small quantities, a fact which doubtless considerably modifies its action upon sensory nerve-endings in the duodenal mucosa. Soper's experiments, in which magnesium sulphate was given orally while the duodenal tube was in place, though designed to prove that magnesium sulphate acts the same whether given by mouth or introduced by the duodenal tube, are subject to criticism, because the presence of the tube in the pylorus may render the latter incontinent and thus greatly modify the regular conditions of oral administration.

If the opinions here discussed concerning the physiology of the Meltzer-Lyon test be accepted, this test may be considered a functional test of the gall bladder. We have recently shown that the gall bladder is primarily a contractile reservoir. The Meltzer-Lyon test, when interpreted as we interpret it, permits estimation of the gall bladder's contractility and thus supplies very important information. The lack of precise physiopathology existing hitherto has limited this test to determining whether the normal communication between gall bladder and common duct is patent or not, and whether or not the gall bladder is infected, the latter point being shown by cytologic and bacteriologic examination of the bile.

Henceforth, not only may these two points be determined, but the test will permit estimation of the contractile capacity of the wall of the gall bladder and reveal the presence of new syndromes of atony, stasis and perhaps hypertonus of the gall bladder. Hypertonus as existing pathologically in hepatic colic and postprandial diarrhea still further supports the physiologic conceptions which we have here presented.

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ETIOLOGY AND PATHOLOGY OF PEPTIC ULCER.*

By Samuel Levine, M.D.,
BROOKLYN, N. Y.

I use the term peptic ulcer advisedly to signify those ulcerations in which digestive processes form an etiologic factor. The very word peptic, which is derived from the Greek "peptiros" (to digest), suggests the fact that the process of digestion here plays a role. Quincke[1] in 1879 used the term ulcera peptica for the first time.

Thus when we speak of a peptic ulcer we mean any ulceration in the formation, or continuation of which, gastric juice plays a part. Gastric juice may cause an ulcer under certain conditions (Bolton,[2] Mann and Kawamura,[3] Mann and Williamson[4]); it may also prevent its healing (Virchow, Bolton, von Bergmann).

Peptic ulcer occurs in the stomach, duodenum, and rarely in the lower end of the esophagus. It may also occur in the jejunum after a gastroenterostomy and it may be found in the duodenum or jejunum when the pancreatic and bile ducts have been transplanted to a lower portion of the ileum, thus depriving the upper portion of the small intestines of the alkaline secretions of the liver and pancreas. It is significant that such ulcers are found only in those organs which come in contact with acid gastric juice (Mann and Williamson[4]).

It is admitted by all who have thought and worked on this subject that a peptic ulcer starts as a simple erosion or loss of living substance. From Rokitansky[5] to Rosenow,[6] pathologists, clinicians and laboratory workers all admit this to be a fact. Indeed it is impossible to conceive how it could be otherwise. What is not always understood is the fact that the causes which give rise to an erosion need not be the same as those that transform the erosion into a peptic ulcer. This distinction must be made in order to have a clear understanding of the etiology of peptic ulcer. We shall therefore consider: (1) Etiology of erosion; (2) the factors that operate to transform the erosion into a peptic ulcer.

Before we proceed with their etiology let us first consider their morbid anatomy.

What is an Erosion? It is a loss of substance of the mucous membrane involving, as a rule, only the mucosa and the superficial layers of the submucosa. Rarely does it penetrate the muscularis propria, and it is extremely rare indeed that it penetrates all the layers of the organ and causes a perforation. Fibrosis is never present at its margins or its base—this is characteristic. It may or it may not be surrounded by an inflammatory reaction with

* Read at a meeting of the Junior Staff of the Brownsville and East New York Hospital, Brooklyn, September 29, 1925.

an infiltration of polymorphonuclear leukocytes. It need not even present an excavation in its wall; it may merely show a necrotic area.

An erosion goes through various changes before it develops into a peptic ulcer as we see it in man. The blood covering it is digested by the gastric juice and leaves its base clean. It also digests the fibrous tissue and muscle fibers of its margins and base, thus causing it to spread in depth and width. It is irritated by hydrochloric acid and possibly also by bacteria, in this way producing a necrotic layer and, later, sclerotic fibrous tissue. At first these changes are slight, but they increase as the action of the gastric juice continues. Bolton[2] divides ulcers into acute, transitional, and chronic, each variety corresponding to a stage in the development of peptic ulcer from a simple erosion. For our purpose such a classification is quite unnecessary and may even lead to confusion of terms, because an erosion may then be called an acute ulcer and *vice versa*. A perusal of the literature on this subject written during the last seventy years will convince anyone of the truth of this statement. Furthermore, it has been shown experimentally (Rosenow,[6] Mann and Williamson[4]) and clinically (Crohn[7]) that a typical callous peptic ulcer may be formed within three weeks. Therefore all practical purposes are served when we consider a peptic ulcer one in the formation or continuation of which gastric juice plays a role.

What is a Peptic Ulcer? It is a defect in the wall of the viscus, practically always involving the muscularis propria and characterized by the presence of fibrous tissue at its margins and base. It is surrounded by lymphocytes and frequently by eosinophiles. Endarteritis and phlebitis are often seen about the ulcer. Sometimes a thrombus is formed which may subsequently undergo canalization. Changes in the bloodvessels may be due to an infiltration of cells in the adventitia, blocking the vasa vasorum and in this way interfering with the blood supply of the vessels (Kaufmann[8]). Its base may be soft and cellular, or it may consist of sclerotic fibrous tissue depending on its chronicity. It may be covered by a necrotic layer which in turn may be hidden by a layer of leukocytes and fibrin. In the typical gastric ulcer, which is generally seen on the lesser curvature near the isthmus, the necrotic layer is most often found on its oral side.

Etiology of Erosion. There is nothing mystical in the production of erosions in the stomach or duodenum. Any single factor, or any combination of factors, that will produce erosions in the skin or in any other organ for that matter, may produce erosions in the stomach, duodenum, and so forth.

Mechanical, Physical, and Chemical Causes. A common illustration of the production of ulcer by trauma is the case of young nursling calves which are taken prematurely from their mothers'

breasts and given food which has not been well ground. These calves almost invariably develop erosions of the stomach, some of which are converted into real peptic ulcers. On the contrary, calves not subjected to such improper food did not present these findings. Also, when stomachs of mature cows were examined, they presented normal mucous membranes because by the act or rumination they bring up their food into the mouth, saturate it with saliva, masticate it over and over again and therefore render it noninjurious to the gastric mucosa. (Gruber and Kratzeisen,[9] Bongert[10].)

Rosenow was told by employees of the Chicago stock yards that gastric ulcers are found in animals most often during late winter and early spring because at these seasons fodder is particularly coarse.

Under this heading we must also put cases of gastric ulcer which develop after blows on the stomach. Potain,[11] Thiem,[12] Dietrich,[13] Griffiths,[14] Hoffman,[15] Leube[16] and Ritter[17] have reported and discussed such cases. Ritter produced erosions in the dog's stomach by blows over the gastric region. This most frequently resulted when the stomach was full. He is of the opinion that belts and tightly laced corsets may produce erosions in the stomach by interfering with its blood supply. This, according to him, explains the frequency of gastric ulcer in women. Faulty posture, compressing the stomach and thus interfering with its blood supply, may explain its frequency among jewelers, tailors, shoemakers, and so forth.

Schwarz[18] emphasizes the importance of the waist (the space between the rigid costal margin and the rigid iliac bone). The pressure exerted in this area by the abdominal muscles on the stomach, forcing it against the spine, results in erosions. This was borne out by his observations that in gastroptosis, where the waist presses upon the lesser curvature, he found the ulcer on the lesser curvature, while in tonic, steerhorn stomachs which are situated high, and where pressure is exerted on the pylorus and the first portion of the duodenum, the ulcers were found on the pylorus or the duodenum. (Fig. 1.)

The effects of high temperature in producing ulcer is nicely shown by the experiments of Decker[19] who produced erosions and ulcers by feeding dogs with gruel at a temperature of 50° C. These ulcers are not due to scalding but to congestion of the mucous membrane with increased peristalsis. This results in increased contraction of the gastric musculature upon the congested vessels, interfering with the venous circulation, and producing hemorrhagic erosions. This explains the frequency of gastric ulcers in cooks. Heiser[20] found that in 108 cases of peptic ulcer that came to operation, practically all gave a history of having eaten very hot food.

That chemicals, such as strong acids and alkalis result in erosions of the stomach and duodenum is a matter of common observation

and requires no further discussion. Bolton found that 0.5 per cent of acetic acid materially enhances the action of gastrotoxic serum in the production of gastric ulcers in animals. When one considers that this is only one-eighth the strength of vinegar, it is easy to appreciate the harm the latter will do under certain conditions. Acetic acid, when more than 2 per cent in strength, is poisonous. The normal gastric mucous membrane successfully withstands the quantity of hydrochloric acid produced even during hypersecretion. But if its vitality has been impaired it is unable to resist its deleterious effects, and gastritis and erosions may ensue. Spasm with retention, or irritating food (for example, vinegar) in combination with hypersecretion may be strong enough to produce the same results.

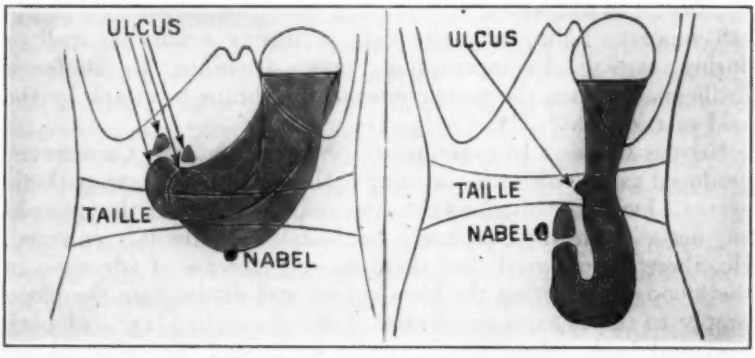

FIG. 1.—Location of ulcer on lesser curvature in gastroptotic stomach and on pylorus or duodenum in tonic stomachs. (Adapted from Schwarz.)

Circulatory Causes. Virchow[21] thought that gastric ulcer is preceded by circulatory disturbances in its mucous membrane which deprived the area involved of alkaline blood; this area is thus exposed to attack by the acid gastric juice. Such disturbances may be due to portal stasis, contraction of the stomach musculature upon engorged bloodvessels, or diseases of the bloodvessels themselves. He found that the vessels which are superficially placed are most vulnerable. These are the coronary, short gastric, and the gastroepiploic arteries. Müller[22] produced erosions in the stomach by tying the portal vein. Buday[23] and Hamburger[24] emphasize the important role played by arteriosclerosis in the production of gastric ulcer.

It was thought that the funnel shape of a gastric ulcer could be explained by the formation of an infarct in the wall of the stomach produced by obstruction to the flow of blood in one of its vessels; this might be due to an embolus, thrombus, or arteriosclerosis.*

* This view was attributed to Virchow by Decker,[19] Bolton,[25] Stewart,[26] and others, but after a careful perusal of Virchow's text I found no such statement.

But it was found when the bloodvessels in the region of the ulcer were examined that the course of the branches did not at all coincide with the location and shape of the ulcer (Aschoff[27]). Furthermore, inasmuch as arteriosclerosis is most common during and after middle age, and as peptic ulcer is very common among the young, it follows that arteriosclerosis cannot be considered an important cause, at least among the young. Furthermore, the fact that ulcers bleed so frequently is another argument against it, since occluded vessels do not bleed. Besides, in erosions the vessels are found to be undamaged; it is only when the erosion has developed into a peptic ulcer that pathologic changes appear in them. Bolton says, "The presence of clots in small arteries at the base of an ulcer are secondary phenomena, and in rare cases in which a clot has been found in a large vessel near an ulcer there is reason to believe that such a clot is secondary."

Temporary failure of circulation, as during a fainting spell or during cardiac decompensation, may, according to Professor Erdheim, lay open the gastric mucous membrane to attack by the acid gastric juice.*

Nervous Causes. In experiments performed in 1828 Cammerer[28] produced gastric ulcers by injuring both vagi and both sympathetic nerves. Durante[29] obtained the same results by ligating the splanchnic nerves. In these animals he found the adrenals enlarged. He, therefore, inferred that there was an increase of adrenalin in the blood, constricting the bloodvessels and diminishing the blood supply to the mucous membrane of the stomach. Ivy[30] cut both vagi and both splanchnics and also extirpated the celiac plexus without producing any ulcers. He accounts for his negative results by the fact that he fed his animals carefully. In his opinion injury to these nerves does not produce ulcers. When their feeding is neglected, their general resistance is lowered and the bactericidal action of the gastric juice is diminished, due to a decrease in the free hydrochloric acid. The bacteria are thus given a chance to invade the stomach and set up an inflammation resulting in ulcers. Günsberg[31] in 1852, said that hypersecretion of hydrochloric acid produced by nervous influences is the direct cause of gastric ulcer. According to Beckey[32] continuous spasm in the fundus may result in ulceration at the point opposite because of the resistance offered to the gastric contents in the lumen thus narrowed. In 1869, Klebs[33] considered spasm of the muscular coats of the gastric arteries as the primary cause of erosions of the stomach.

The most recent advocate of the spasmogenic theory is von Bergmann.[34] He begins with the proposition that "functional disturbances may produce anatomic changes." This is borne out by the extraordinary frequency with which peptic ulcers are found in lead workers (Schiff). It is well known that lead poisoning is accom-

* Verbally communicated.

panied by spasm which manifests itself in the form of colic, constipation, asthma, and so forth. Elsching also found transient blindness in lead workers due to spasm of the retinal bloodvessels. Exner studied 10 cases of tabes dorsalis with degenerative changes in the subdiaphragmatic branches of the vagus; 6 of these had peptic ulcers. That injury done to the vagus and sympathetic nerves will produce ulcers has been abundantly proven. Erosions found in meningitis and after operations on the brain are, according to von Bergmann, also due to nervous influences. No one will deny that spasm is frequently present in the stomach. Contraction of the greater curvature opposite an ulcer is due to spastic irritation. This has been likened to a finger pointing to the seat of trouble. Haudek observed that the size of a niche varies from day to day, depending on the spastic condition of the stomach. Surgeons notice that by stroking the stomach serosa they produce a white anemic area. This is due to contraction of the bloodvessels which assume the form of white lines having a stellar arrangement. In gastric surgery done under local anesthesia, peristalsis still takes place (contrary to general anesthesia). During these contractions the ulcer region is blanched due to spasm of the bloodvessels. All this proves that spasm in the stomach is a reality. It may be localized in the muscularis propria, muscularis mucosa, or in the bloodvessels. It is easy to infer that if one of these spasms lasts long enough, an area of ischemic necrosis will ensue. We then have an erosion which may subsequently develop into a peptic ulcer. By means of spasmogenic drugs (physostigmin, pilocarpin) Westphal[35] and others produced erosions in the stomach; he also demonstrated spasm of the muscularis mucosa and muscularis propria. Von Bergmann considers disturbed innervation as the cause of hypersecretion and hyperperistalsis, so frequently encountered in peptic ulcer. Continued spasm delays healing because it diminishes the supply of blood to the ulcer. Ulcer pain may be due to spasm or exhaustion of the gastric musculature following spasm.

Contrary to the statement made by Boas, von Bergmann does not base his theory on the conclusions arrived at by Eppinger and Hess[36] in their studies of the vegetative nervous system. Vagotonia and sympathicotonia are, according to them, altered states of these respective nerves; these frequently explain obscure clinical phenomena. Von Bergmann is emphatic in his denial that they have any clinical value. He is of the opinion that the extravagant statements made by Eppinger and Hess tend to ridicule the theory that nervous influences have anything to do with the production of peptic ulcer.* We know so little about the innervation of the stomach, the relations of the vagus and sympathetic nerves to the plexi

* "Vagotonia and sympathicotonia cannot be made use of in the clinic."
"The terms vagotonia and sympathicotonia must be absolished."
"Those attempts that went too far—particularly the attempt of Eppinger and Hess—have undoubtedly brought confusion and discredited the (nervous) theory." —von Bergmann.

of Meissner and Auerbach that the best we can do is simply to put this theory on a general basis and avoid detailed but unproven particulars. Injury anywhere along the path of innervation, preganglionic, postganglionic, synapsis, plexi of Auerbach and Meissner, or at the neuromuscular organ, may produce the results described above. The first portion of the duodenum, so often the seat of peptic ulcer, is easily influenced by spasm. It is a matter of common observation that spastic deformity of the duodenal cap is not only seen in duodenal ulcers but quite as often in gastric ulcers, cholecystitis, chronic appendicitis, or any other intra-abdominal disease. The theory of von Bergmann takes cognizance of the existence of two facts—ulcer and spasm—and explains one by the other.

Rössler[37] claims that peptic ulcer is always secondary to some other abdominal disease, such as appendicitis, cholecystitis, adnexitis, and so forth, and that the spasm spoken of above is due to reflex disturbances from "the primary disease."

In a large number of cases of peptic ulcer studied by Singer[38] he found large tuberculous mediastinal glands. These compress the vagus, irritate it, disturb the innervation of the stomach, and cause functional disturbances which may give the clinical picture of ulcer. Even hematemesis may result without any distinct anatomic changes in the stomach or duodenum. In his opinion persistent functional derangement may result in organic changes with formation of peptic ulcers. Degenerative changes of the vagi in these cases were demonstrated by him and others.

General Causes. This includes a large number of vague conditions, the effects of which on the production of peptic ulcers have by no means been proven. Such, for example, are the terms "constitutional and hereditary causes," "psychic causes," and so forth. Enteroptosis was also credited with being an important causal factor. However, only about 16 per cent of all gastric ulcers show this condition (Boas[39]). Chlorosis was long thought to be a cause of ulcer, but this has been definitely disproven by Bolton. Still, it must be admitted that secondary anemia may predispose to the formation of ulcer and delay its healing. This is borne out by the experiments of Quincke and Dättwyler[40] who have shown that animals rendered anemic by repeated bleedings were more likely to develop ulcer from any cause and have their healing delayed than normal animals. Virchow,[21] Ritter[17] and Aschoff[27] argue that general causes produce general effects, and since peptic ulcer is a distinctly local condition (92 per cent of all gastric ulcers and 84 per cent of all duodenal ulcers are single—Stewart[26]) local causes should be held responsible for their formation.

Antipepsin Theory. The old question why the gastric juice does not digest the stomach continues to give rise to one of the most stimulating controversies in the annals of medicine. John Hunter,[41]

in 1772, advanced the theory that a vital principle present in all living tissue prevents its digestion. But Claude Bernard[42] in his classical experiment has shown that the leg of a living frog is digested in the stomach of an animal, thus disproving Hunter's theory. Bernard assumed the existence of an antiferment in the gastric mucous membrane which prevents its digestion. Danilewski[43] extracted antipepsin from the gastric mucous membrane with a weak solution of hydrochloric acid. Weinland[44] has shown that worms which live in the stomachs of animals are resistant to the action of gastric juice even after they are killed. Katzenstein[45] found that a loop of small intestine with its blood supply intact, when transplanted to the stomach, is quickly digested. This also takes place if the lower pole of the spleen or the appendix, with its blood supply unimpaired, are introduced into the stomach. But when the first portion of the duodenum or a flap of the stomach wall is inserted into the stomach, no digestion takes place. Furthermore, even dead duodenal (first portion) and gastric tissue are resistant to the gastric juice. This proves the presence of an antipepsin only in the walls of the stomach and the first portion of the duodenum. By decreasing the quantity of antipepsin in the mucous membrane of the stomach, he produced typical callous ulcers.* He, therefore, assumed that peptic ulcer is produced by a deficiency of antipepsin in the gastric mucous membrane. Wolff[46] found no decrease of antipepsin in the stomachs of ulcer patients. Kawamura[47] found antipepsin in all living tissue. He repeated the experiments of Katzenstein taking special care not to injure the circulation of the flap inserted in the stomach and found that even intestines, spleen or other organs were not digested. He concluded that living tissue is not attacked by gastric juice so long as no circulatory disturbances are present. Peptic ulcer would thus be due to interference with the circulation at the affected area which prevents antipepsin from reaching it. Kohler[48] compared the antipeptic acitivity of the blood of ulcer patients with the peptic activity of their own gastric juice, and found that the second by far exceeded the first; while in those free of ulcer, the first exceeded the second. Making use of this method, he arrived at a correct diagnosis in almost a 100 per cent of his cases. Orator[49] used the method advocated by Kohler, and in a study of 50 cases was unable to verify his findings. Lieblein[50] found that the quantity of antipepsin in the blood of normal cases is constant, while in those with ulcer, it is either very high or very low. Gunzburg[51] found an increase of pepsin in the stomach contents of ulcer patients, while in those free of ulcer he found it to be normal.

This interesting phase of the ulcer problem is still unsettled, in spite of the fact that it has attracted the attention of the most

* So stated by Boas.[39]

illustrious medical minds of the last one hundred and fifty years. However, from these experiments the conclusion may safely be drawn that antipepsin is present at least in the stomach, and that this prevents the stomach from digesting itself.

Aschoff's Theory. Aschoff[27] divides erosions into two varieties.

(*a*) *Fundic Erosions.* These are large in number, small in size, and have their base covered with blood. They are found in all cases where vomiting takes place (for example, in meningitis and following abdominal operations). His explanation of their formation is as follows: Every act of vomiting is preceded by hyperemia, which is followed by contraction of the musculature of the stomach upon the engorged vessels. As a result of this, they rupture, and so produce small areas of hemorrhagic necrosis. This view is very similar to the one expressed by Rindfleisch[52] in 1872 who said, "The act of vomiting, by temporarily resisting the return of blood, causes minute extravasations from the superficial venous radicles of the gastric mucous membrane," in this way producing erosions. These heal very rapidly. They are produced in the laboratory by the administration of spasmogenic drugs, such as pilocarpin and physostigmin. They are also produced by section of the vagus.

(*b*) *Erosions Found at the Lesser Curvature.* These are few in number and large in size, both in width and depth. They are rarely found together with the fundic erosions, thus indicating that their causes are different. They do not heal as readily as the first variety. Aschoff assumes that spasm of some unknown origin is the cause of these erosions, although spasmogenic drugs do not produce them. This he explains by the fact that the Magenstrasse has its own muscular system and its own nerve supply the details of which are known but very little. In this connection it is interesting to note that Ottfried Mueller[53] examined the capillaries, arterioles, and venules of the skin and inner surfaces of the lower lips of ulcer patients, and found anatomic as well as physiologic changes (motor as well as secretory). In resections of the stomach done for ulcer and cancer, he had clamps applied to each end of the resected part to prevent blood from flowing out, and he found that in cases of gastric ulcer the changes in the capillaries, arterioles, and venules, while present in all parts of the stomach, were most marked in the Magenstrasse. In carcinoma of the stomach no such changes were found. Mayer-List[54] corroborated Muellers' findings.

Theory of Inflammation. This subject divides itself into two branches.

(*a*) *Anatomic Evidences of Inflammation.* Cruveilhier[55] compared gastric ulcers to typhoid ulcers in the intestines. Since the latter begin as an inflammation of the lymph follicles he assumed that the first also originated in this manner. Konjetzny[56] observed that gastritis frequently accompanies gastric ulcer. The question then arises, is there a causal relation between the two, and if so, which

is cause and which is effect. Aschoff is of the opinion that gastritis is secondary to ulcer because living tissue is not digested by the gastric juice, and because it is frequently present in carcinoma of the stomach, a condition which, he thinks, is rarely accompanied by ulcer. Bolton, however, as a result of his experiments came to the conclusion that gastritis may give rise to ulcer, although frequently it is caused by ulcer. He constricted the duodenum in animals, producing gastric retention, and then fed them with hydrochloric acid (0.4 to 0.7 per cent). In a large number of them gastritis developed, in many of which this condition led to ulcer formation. In humans, spasm of the pylorus or the duodenum, giving rise to gastric retention, is frequently accompanied by hypersecretion. We then have naturally the same causes of gastritis as those artificially produced by Bolton in his experimental animals. It is, therefore, very probable that in some cases at least, gastric ulcer may be due to gastritis. Since spasm and hypersecretion may cause gastritis, and since they are frequently a result of gastric ulcer, it follows that gastritis may be caused by ulcer. The two conditions may also coexist independently, both being produced by the same cause.

Aschoff called attention to the presence of pyloric and even intestinal glands in the acid-bearing area of the stomach. It is very likely that they are due to metaplastic changes following healed erosions. Whether they may become the seat of an ulcer as a result of their anomalous position has not been settled.

(*b*) Of greater significance than the study of anatomic changes in the gastric mucous membrane are the bacteriologic experiments and findings of recent years. Askanazy[57] found the Oïdium albicans in 25 out of 30 cases operated for peptic ulcer. He also injected animals with a substance scraped from the ulcer base. In one-half of these he succeeded in producing ulcer, and in one-half of the ulcers so produced he found the Oïdium albicans. This question is as yet not settled. Aschoff believes that the Oïdium albicans is a secondary invader. Lebert,[58] in 1857, injected pus into the veins of animals, in this way producing general pyemia. The stomachs of these animals showed numerous erosions. Cohn[59] in 1860 produced erosions by the injection of bacteriæ into the bloodvessels of animals. In 1888, Letulle[60] and also Widal[61] produced the same results by the same means. Böttcher,[62] in 1874, was the first one to isolate bacteriæ from the margins of the ulcer base. In 1907, Rosenau and Anderson[63] produced erosions by injecting diphtheria toxin into the blood. This proves that the production of ulcers by bacteria need not be due to bacterial emboli lodging in the vessels. Bolton is of the opinion that bacterial infection is the most common cause of localized interstitial hemorrhage which leads to hemorrhagic erosion and subsequently to the formation of gastric ulcer. The sudden spreading of a chronic gastric ulcer may, in his opinion,

be the result of infection. He said, ". . . an existing and perhaps unsuspected local infection of some organ" may be the cause of a chronic peptic ulcer. In 1913 Rosenow[6] injected intravenously into animals a streptococcus of sufficiently low virulence not to cause a general infection, and he found that in a number of these animals, erosions and ulcers of the stomach and the duodenum were produced. Not only that; he was able to culture from these erosions a strain of streptococci which, when reinjected into animals, reproduced the same lesions. In this way he has proven the "elective localization" of these bacteriæ. Furthermore, bacteriæ isolated from the duodenum tended to localize in the duodenum, while those isolated from the stomach tended to localize in the stomach. The ulceration was the result of a localized infection with secondary digestion. In infection of the gastric mucous membrane, according to him, there is a disturbance in the mechanism of gastric secretion. Normally, hydrochloric acid is produced on the surface of the stomach, but when the stomach is infected, hydrochloric acid is produced in its wall, thereby causing its digestion. He isolated streptococci from gastric and duodenal ulcers in man, or from foci of infection (teeth, tonsils, and so forth) in ulcer patients, and after injecting them into animals he reproduced typical callous ulcers. Streptococci obtained from these ulcers, when reinjected, again produced such ulcers. Ivy[30] produced erosions in the stomach of animals by pinching the gastric mucous membrane, and then fed them with bacteriæ. He found that peptic ulcers developed only in those that were in poor general condition. These had but little free hydrochloric acid which gave the bacteriæ a chance to infect the stomach wall, and consequently produce ulcers. The injection of streptococci (viridans and hemolyticus) in branches of the gastro-epiploic arteries did not produce ulcers. Recently, experiments performed by Russell, Haden, and Bohan,[64] also Scott, Loria and Haden,[65] corroborate most convincingly the findings of Rosenow.

Allergic Causes. Bolton[2] prepared a gastrotoxic serum by injecting a rabbit intraperitoneally or subcutaneously with an emulsion or saline extract of the fresh gastric mucous membrane of a guinea pig. This was repeated at ten day intervals. The cells of the guinea pig stimulate the tissues of the rabbit to produce a substance which destroys the foreign invaders. However, the rabbits' tissues produce an excess of this substance and whatever remains after the enemy has been repelled is found freely circulating in the blood of the rabbit, ready for attack wherever the enemy may be met. The experimenter may bring together the opposing forces by mixing in a test tube some of the rabbit's serum with the gastric mucous membrane of the guinea pig in which case the cells of the guinea pig are rapidly destroyed. Or he injects some of the rabbit's serum into a living guinea pig; then, besides the general phenomena of allergy and anaphylaxis, local destruction of tissue

is produced in the entire gastro-intestinal tract, but this is most marked in the stomach. By the same method, Bolton obtained a gastrotoxic serum from the goat, active against the cat by introducing its gastric mucous membrane into the goat. In his experimental production of gastric ulcer, Bolton most often used his gastrotoxic serum locally, that is, he injected it directly into the stomach wall and in this way produced ulcers. These experiments are certainly very interesting from a purely scientific point of view, but it is difficult to see how they ever apply to man. The animals he used were those of heterologous species, and as Karsner,[66] says, "In order for this to be applicable to man, it will be necessary to prepare serums by injection, not only into the homologous species, but into the same animal. In other words, there must be not merely an isogastrolysin but an autogastrolysin. We have been unable to produce such a serum, and on the basis of other immune phenomena, regard it as an experiment with well nigh insurmountable difficulties."

Of greater significance in this respect are the experiments conducted by Ivy and Shapiro.[67] They sensitized an animal to a foreign protein (egg albumen, beef protein, oat protein, and so forth), and then injected that protein locally into the gastric mucous membrane. In this way they produce acute ulcers which healed within two to three weeks.

In reviewing the causes of erosions in the stomach and the duodenum it is obvious that almost any of these may produce erosions in any other organ of the body. Chemical, mechanical, and thermic factors, interference with circulation or innervation, infection, and allergic phenomena, will destroy tissue in any organ.

Transformation of Erosion into Peptic Ulcer. The first half of this paper has been devoted to a discussion of erosion which is the first step in the formation of a peptic ulcer. Thus the causes of erosion are in part the causes of ulcer. It has, therefore, been impossible in this paper consistently to keep these terms apart, particularly since earlier investigators whose work is included in this discussion failed to make this distinction.

We are now ready to deal with the question: What circumstances convert an erosion into a peptic ulcer? In answering this we find that there are two factors at work here: (1) The acid gastric juice, and (2) the peculiar structure of that part of the stomach known as the gastric pathway (Magenstrasse).

The Acid Gastric Juice. (*a*) In the jejunum, peptic ulcer never occurs as long as the chyme runs through the normal channels and its acid contents are neutralized by the alkaline secretions of the liver, pancreas, and duodenum. Only when this is prevented by direct communication between the stomach and jejunum (gastrojejunostomy) does peptic ulcer occur in the jejunum.

(*b*) Mann and Kawamura[3] resected the duodenum in dogs, anastomosed the stomach with the jejunum and transplanted the bile and pancreatic ducts to a lower portion of the small intestines. In 2 of the 10 dogs thus treated, typical peptic ulcers appeared on the jejunal side of the gastrojejunal anastomosis.

Mann and Williamson[4] transplanted the pancreatic and bile ducts to the ileum, leaving the duodenum in some animals and resecting it in others. They found "that typical subacute or chronic peptic ulcers quite comparable pathologically to that found in man, developed in the intestinal mucosa just adjacent to the gastric mucosa in a high percentage of cases." In these experiments, Mann, Kawamura, and Williamson, have produced in the laboratory animals the same condition that results in man after a gastro-enterostomy. In both instances, acid chyme is introduced into a viscus naturally unfit to receive it. This results in digestion of its walls and production of peptic ulcers.

(*c*) Bolton[2] found that gastrotoxic serum did not cause ulcers in the presence of more than 1 per cent of sodium bicarbonate in the stomach. Even microscopic examination of the gastric mucosa failed to reveal any pathologic changes. He has also shown that acute ulcer is much more easily produced in the digesting than in the resting stomach, and that ulceration produced in the presence of hyperacid stomach contents is much more extensive than ulceration produced in normal stomach acidity.

(*d*) Gastro-enterostomy done in carcinoma of the stomach does not result in jejunal ulcer, doubtless as a result of the absence of acid gastric juice.

(*e*) In almost 40 cases of pernicious anemia that came to autopsy,[26] no gastric ulcers were found, in spite of the fact that anemia favors ulcer formation. In this condition achylia gastrica is the rule, and unless a gastric ulcer was present before the onset of pernicious anemia there is no reason for finding it.

(*f*) Peptic ulcers are found only in that part of the gastrointestinal tract which is in contact with acid gastric juice. Nothing like it is to be found along the entire digestive canal unless acid gastric juice is or was in contact with it.

(*g*) Von Eiselsberg devised an operation for the relief of ulcer which consists of posterior gastroenterostomy with pyloric exclusion. It[68] was found that a stomach so treated secretes a juice of great acidity, and as a result of this jejunal ulcers with fatal hemorrhages were extremely common. On the other hand, the benefit derived from subtotal gastrectomy (von Haberer and Finsterer) is largely due to diminished acid production.

"Chronicity of ulcers" says Aschoff,[27] "depends on the action of the gastric juice;" and Bolton,[2] "ulcer is produced by the action of the gastric juice." However, the chief culprit is the hydrochloric acid. This is proven by Bolton's experiments, in which he produced

follicular erosions, and subsequently peptic ulcers, by feeding animals with hydrochloric acid in the presence of gastric retention (constriction of duodenum). Bolton found that even normal gastric juice may produce ulcers, provided that the gastric mucous membrane has been devitalized. Actual death of cells is not a necessary requirement. It is the hydrochloric acid which delays the healing of erosions, destroys its base, and covers it with a necrotic layer. It stimulates the production of sclerotic fibrous tissue which has a poor blood supply. Epithelium must have a suitable place on which to grow, and the gastric glands need a soft stroma that they may penetrate it and develop. Necrotic masses, or sclerotic fibrous tissue, provide no nutrition for the young and tender cells eager to cover the base of the ulcer.

Rosenow denies that hydrochloric acid plays so great a role in the formation of ulcers of the stomach or duodenum. His arguments are:

1. Hyperacidity may exist for years without producing ulcer. This is quite true, but in the presence of gastric retention, improper food, or lowered vitality, hyperacidity is likely to result in ulcer (Bolton's experiment). But what is even more certain is the fact that an erosion, however produced, may be converted into an ulcer by the hydrochloric acid (Virchow, Bolton, Aschoff, von Bergmann, Mann, Kawamura, and Williamson).

2. Defects in the stomach heal promptly after excision, injection of corrosive chemicals, interference with blood supply, or after operations. That most erosions heal is obvious. Elsner[69] was impressed by the frequency with which erosions are seen through the gastroscope even in cases that give no symptoms at all. That the gastric mucosa with its fine cylindrical epithelium successfully withstands the rough usage of coarse ingested particles, driven against it by peristaltic waves, is truly remarkable. It is apparently provided by Nature against such misuse, since erosions, if formed at all, heal rapidly; otherwise, ulcers would be much more common. However, they do not all heal. After an excision of an ulcer, or after a gastroenterostomy, new ones occasionally form in the suture line due to incomplete coaptation or loosening of the suture. Aschoff found that jejunal ulcers formed most often where the clamps had been applied, and Ivy[70] confirmed this in experimental gastroduodenostomies. In these instances the erosions produced by mechanical means were converted into ulcers by the action of the gastric juice.

3. Ulcers occur in achylia gastrica. But achylia may be a result of gastritis which may be secondary to ulcer. Therefore, when achylia is accompanied by ulcer we may assume that the ulcer existed before the achylia. Still, it is admissible that in the absence of hydrochloric acid, bacteria may invade the stomach and produce a purely infectious ulcer. But this is extremely rare, and has

nothing in common with peptic ulcer. Furthermore, the fact that the lymph glands which drain the stomach and duodenum are rarely found enlarged in cases of peptic ulcer, speaks against its infectious nature.

4. Why do fundic erosions heal readily although they are right in the midst of the acid-secreting portion of the stomach? This is due to the structure of the fundus which favors healing. It will be discussed at length in the next section.

5. Ulcers are most common in the pyloric canal and in the duodenum where acid cannot be very concentrated. Resistance is offered to the gastric contents at the isthmus, pylorus, and at the narrow and spastic first portion of the duodenum. This traumatizes their walls, and so prevents healing.

The pioneer work of Rosenow, since substantiated by many experiments, proves beyond doubt the causal relation between bacterial infection and erosions in the stomach and duodenum. However, it is the hydrochloric acid in combination with the peculiar structure of the Magenstrasse that prevents their healing and transforms them into peptic ulcers.

Ivy[30] found that a diminution of hydrochloric acid favors ulcer formation after ingestion of bacteria. But "nutritional disturbances and lowered resistance" were also present. And Bolton has shown that these conditions favor ulcer formation by hydrochloric acid. Besides, an increase of hydrochloric acid is not necessary to attack devitalized tissue. That bacteria may, under certain anomalous conditions, produce gastric ulcer cannot be denied. But the fact remains that peptic ulcer is found only in that portion of the gastrointestinal tract which comes in contact with the acid gastric juice.

The Magenstrasse. (Fig. 2.) Anders Adolf Retzius, who investigated the oblique fibers of the stomach, died in 1860. Two years later his pupil, Gyllenskoeld,[71] described the work of his master in the *Archiv für Anatomie und Physiologie*. The musculature of the stomach consists of three layers: The outer, longitudinal; the middle, circular; and the inner, oblique. These last are best studied in the stomach of the ruminant where they form a complete sphincter, and divide it into four compartments. The bolus of food, when first ingested, goes down to the first and second compartments. It is then brought up for rumination and salivation, after which it slides along the oblique fibers, directly into the third compartment, avoiding the first two. In the human stomach, the oblique fibers form only five-sixths of a sphincter. They surround the cardia like a girdle and run along the anterior and posterior surfaces up to the pyloric canal, where they become a part of the circular fibers. They do not cover the lesser curvature and portions of the anterior and posterior walls adjoining it. Thus a free space is formed above the oblique fibers which is transformed into a groove when they contract. This groove has been named Magenstrasse (gastric path-

way) by Waldeyer. This term is not synonymous with lesser curvature, which means the midline of the stomach when opened at the fundus. Retzius assumed that this groove serves to transmit saliva, fluid and semi-solid food from esophagus to duodenum and that the oblique fibers, by contracting, bring the pylorus closer to the cardia, thus shortening the path traversed by these ingesta. During the act of vomiting, the contents of stomach and duodenum travel the same route, back to the mouth. Claude Bernard[72] noticed that food eaten some time before vomiting took place frequently came up, while that eaten shortly before vomiting was retained. Retzius, therefore, assumed that even the human stomach is divided into locules which are formed by bundles of oblique fibers.

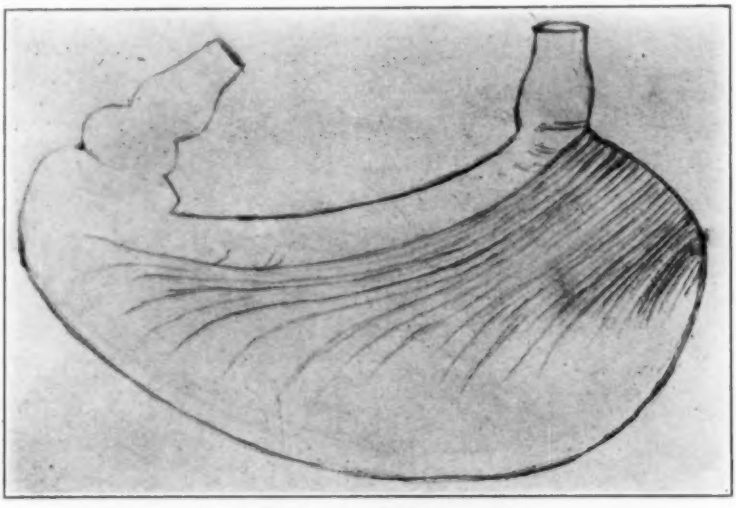

FIG. 2.—Retzius' groove.

Cohnheim,[73] by means of duodenal fistula has demonstrated that when water is administered on a full stomach it runs right out without intermixing with the rest of the food. This confirms Retzius' view of the function of the Magenstrasse. Aschoff[27] is of the opinion that the gastric contents pass through the Magenstrasse before entering the duodenum. By the use of physostigmin, Kaufmann[74] succeeded in demonstrating the Magenstrasse in the dog. It forms a groove which extends from cardia to pylorus, its bottom consists of circular fibers and its walls of oblique fibers. It is two-thirds muscle and one-third free. He has shown conclusively that the Magenstrasse is formed by the contraction of the oblique fibers. Since these are much longer in the human stomach than in ruminants, and occupy more of its anterior and posterior walls, Kaufmann assumes, that, in the former case, even food of

hard consistency runs along the Magenstrasse. It is even very likely that during complete contraction, the oblique fibers may convert the Magenstrasse into a completely closed canal. Volkman[75] found a distinct Magenstrasse in 12 per cent of his 545 autopsies done within four hours after death. He also came to the conclusion that the Magenstrasse may form a closed canal. Aschoff[27] says that the Magenstrasse cannot be demonstrated when the stomach is separated from its points of fixation; it must be fixed *in situ* soon after death or else it will not be seen.

Waldeyer[76] (Figs. 3, 4, 5) has shown that along the inner surface

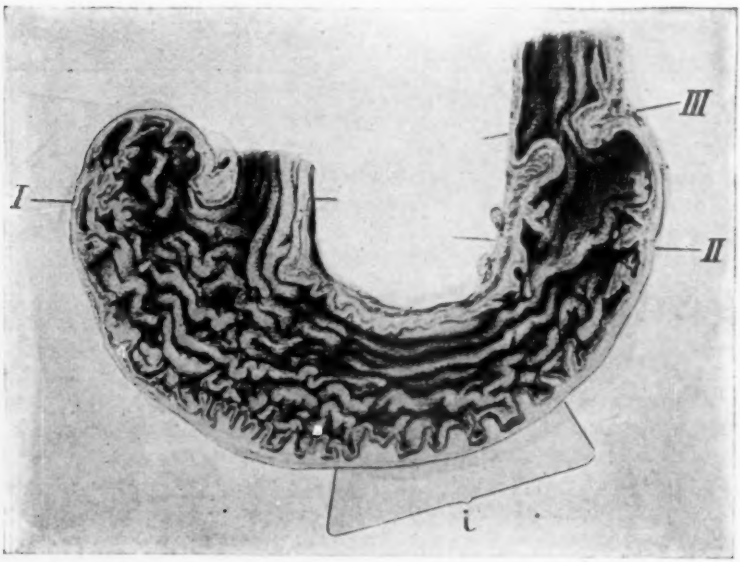

FIG. 3.—Longitudinal section of the stomach. I, Limit between fornix and corpus; II, limit between infundibulum and canalis pyloricus; III, limit between canalis pyloricus and duodenum; *i*, isthmus ventriculi. (Aschoff.)

of the Magenstrasse, four tightly stretched folds run directly from cardia to pylorus without anastomosing with any other folds adjoining them. They consist of longitudinal muscle fibers covered by mucous membrane. The two inner folds are smaller than the two outer ones which cover and protect their weaker neighbors when they are injured much as the omentum covers and inflamed surface, or prevents perforation of an ulcerated viscus. But, when they themselves are injured they remain unprotected. Therefore, most gastric ulcers are located on the outer folds, especially on the posterior one, since the posterior wall of the stomach is comparatively immobile and carries most of the weight of the gastric contents (Bauer[77]).

It is significant that 95 per cent of all gastric ulcers, whether single or multiple, are located in the Magenstrasse. This clinical observation coincides with the results obtained by experiments on animals. Roth,[78] in 1869, fed animals with silver nitrate and found ulcerations in that part of the stomach now known as the Magenstrasse. Stromeyer[79] obtained the same results after administration of caustics, and Decker,[19] after feeding animals with gruel at a temperature of 50° C. Rosenow,[6] in his experiments, found that erosions produced on the fundus tended to heal rapidly, whereas those in the region of the lesser curvature, pylorus, and duodenum

FIG. 4.—The magenstrasse in the dog with erosions. (Aschoff.)

tended to become chronic. Yano (quoted by Aschoff[27]) produced erosions by branding the gastric mucous membrane. He found that they healed readily in the fundus, while in the Magenstrasse they frequently developed into peptic ulcers.

How are we to explain these facts, observed alike by clinician and experimental worker? Is it not likely that the answer to this may be found in the structure of the Magenstrasse? We have already mentioned that it tends to form a distinct canal within the stomach. The longitudinal folds which run along its internal surface are tightly stretched even during peristalsis.* Its mucous

* "The longitudinal fibers" says Cunningham, "are the most powerful over the lesser curvature."

membrane is firmly attached to the underlying tissue (Schmidt,[80] Bloch[81]), while the mucous membrane of the fundus is freely movable. Yano has shown that in the rabbit injury to the fundic mucosa is immediately followed by the production of a mucin-like substance which covers and protects the erosion, that the muscularis mucosa contracts and brings the edges of the wound together much as the surgeon does with the suture, and that epithelization takes place

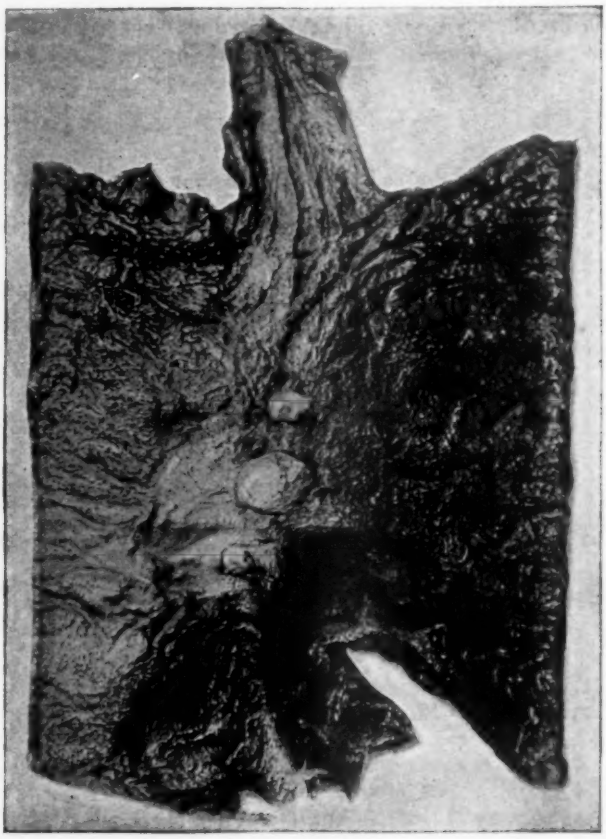

FIG. 5.—Gastric ulcers in the pathway of the stomach. (Aschoff.)

promptly. On the contrary, injury in the region of the Magenstrasse does not result in the production of mucin or contraction of the muscularis mucosa and epithelization, if it occurs at all, is rather tardy. Peristalsis is more active and begins nearer the cardia in the fundus than in the Magenstrasse. It is, therefore, clear that an erosion in the Magenstrasse remains unprotected. There is no mucin to cover it. The adjoining mucous membrane

is immobile and cannot shield it against the corrosive action of the hydrochloric acid. Peristalsis does not reach high enough or is not sufficiently powerful to bring together the edges of the erosion. On the contrary, it is kept open by the tightly stretched folds. The acid gastric juice of the entire stomach pours over its raw surface, irritating and digesting its base, destroying its connective tissue, and covering it with a necrotic layer. The epithelium of its edges, never too willing to proliferate and cover its surface, is now entirely prevented from doing so, because it has no healthy foundation on which to grow. It is small wonder, then, that 95 per cent of all gastric ulcers occur in this region, and that in the Magenstrasse erosions produced by the most diverse methods refuse to heal.

The frequency of peptic ulcer in the first portion of the duodenum may be partly explained by the close anatomic relationship between the Magenstrasse and the duodenum. The powerful longitudinal fibers of the gastric pathway which prevent the healing of erosions by spreading their edges apart, are directly continuous with the longitudinal fibers of the duodenum. Cunningham[82] says that "the longitudinal fibers of the stomach are continuous with the duodenum;" and Howell,[83] "The longitudinal fibers of the pylorus pass over it, to be continued directly with the longitudinal fibers of the duodenum." Furthermore, Akerlund[84] says that irritation due to peptic ulcer produces its strongest effect on the longitudinal fibers. He has shown that in duodenal ulcers, the pylorus is kept open by these fibers, that the irritation is so strong as to prevent the circular fibers of the sphincter, the most powerful muscle of the stomach, from closing. Panner[85] takes exception to this view of Akerlund. He thinks it unproven. However, Reich, of Vienna, considers Akerlund's view confirmed by his vast experience in the Roentgen ray room.*

This view of the Magenstrasse is not accepted by all investigators. Elze[86] found that the longitudinal folds of the lesser curvature end at the incisura angularis and that they do not enter the pylorus. He, therefore, denies the Magenstrasse in the sense in which Waldeyer used the term. Klatsch and von Friedrich[87] conducted a series of experiments to determine whether fluids run along the lesser curvature, and were unable to substantiate this view. On the contrary, they found that fluids mix fairly well with the rest of the stomach contents. Therefore, they contend, there is nothing in the structure of the Magenstrasse to explain the frequency with which ulcers are found here. Of course, this is flatly contradicted by Cohnheim's experiments as described above.

While it is true that the Magenstrasse is the favorite location of gastric ulcers it must not be assumed that all portions of it are

* Verbally communicated.

equally liable. Within the Magenstrasse they occur most frequently at the isthmus and at the pyloric canal. The isthmus is a spastic area situated between the infundibulum and the body of the stomach and usually includes the incisura angularis. Aschoff studied and described it and emphasizes the fact that it is not an anatomic but a physiologic entity. It comes and goes, increases and diminishes in size. It is seen best when the subject is on a mixed diet, but when on a fluid or semisolid diet, it disappears. This explains why it is not seen under the fluoroscope since barium is administered in a liquid or semisolid form. Magnus[88] produced a prominent isthmus by feeding animals on solids. Aschoff[27] has shown that a stomach, if properly fixed postmortem, will not have its isthmus obliterated, even when distended with water. He is of the opinion that it has

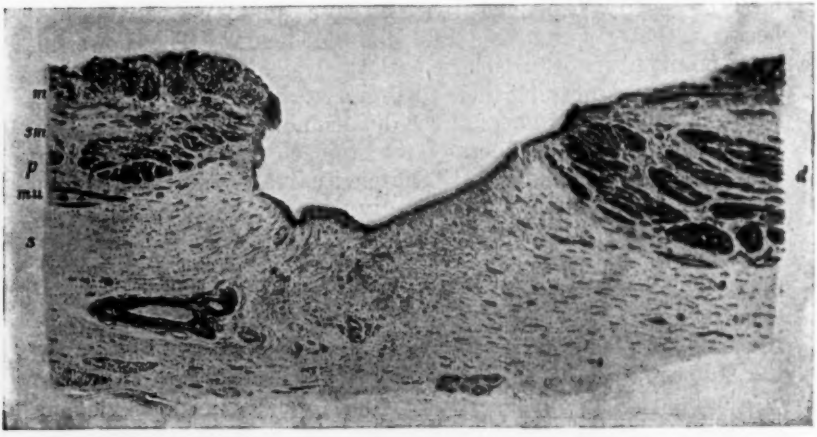

FIG. 6.—Characteristic form of ulcer of the stomach. *m*, Mucosa; *sm*, submucosa; *mu*, muscularis propria; *s*, serosa; *p*, proximal (cardiac); *d*, distal (pyloric). (Aschoff.)

a selective action, permitting only liquefied food to pass, while food that has not been well prepared, is kept back. It also prevents regurgitation into the cardial end of the stomach. In other words, it acts as a pylorus in the middle of the stomach. Bauer[77] considers the isthmus and the pylorus as the "physiologic narrows" of the stomach. Both offer resistance to the passage of food, and are, therefore, traumatized by it, with the difference that the pylorus opens and closes in rapid intervals, while the isthmus stays contracted. Therefore ulcers are more common in the latter. Volkman[75] found that in 11 ulcers of the Magenstrasse 5 were located on the isthmus.

When an ulcer in the isthmus region is carefully examined, it is found that the apex of its funnel is not directed straight downward, but is rather oblique and points toward the cardia (Fig. 6). Further-

more, the mucous membrane of the cardial extremity of the ulcer hangs over it like a precipice, and is undermined by the destructive process going on below it. The musculature at this end is compressed, pointed, and entirely covered by the loose mucous membrane, while at the pyloric end it is exposed and frayed. In the typical case, the pyloric end of the ulcer forms a step-like arrangement (Fig. 7); the step nearest the pylorus consists of mucous membrane, the next one of submucosa, and the third of muscle fiber. This arrangement is so typical that even in an excised ulcer, one can tell which end pointed to the cardia, and which to the pylorus.

How is this arrangement to be explained? According to Aschoff[27] and Stromeyer[79] the flattening of the pyloric part of the ulcer is produced by the pull exerted upon it by the isthmus; while the over-hanging of the cardial side is due to the peristaltic waves which

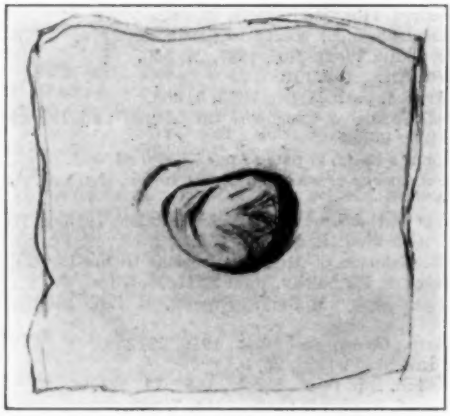

FIG. 7.—Step-like arrangement of floor of ulcer at pyloric end.

carry the mucous membrane along, and leave it hanging over the ulcer cavity. This forms a receptacle for food, saturated with gastric juice which digests the base of the ulcer, prevents its healing, and causes it to spread.

Summary. 1. Peptic ulcer starts as an erosion.

2. Erosions may be produced by mechanical, chemical, or physical causes, circulatory and nervous disturbances, infection, and allergic phenomena.

3. Erosions in the region of the Magenstrasse do not heal readily because of its peculiar structure.

4. Erosions are converted into peptic ulcers by the destructive action of the acid gastric juice.

5. The isthmus, pyloric canal, and first portion of the duodenum, because of the resistance they offer to the acid chyme, are particularly liable to be involved in ulcerative processes.

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THE PERVERTED PHYSIOLOGY OF THE STOMACH AFTER GASTRIC OPERATIONS.

By G. de Takats, M.D., M.S.,

FORMER ASSOCIATE IN SURGERY, UNIVERSITY OF BUDAPEST; ASSOCIATE IN SURGERY, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, CHICAGO, ILL.

At the present time when the surgical treatment of gastric and duodenal ulcers is a much discussed subject, it may be of some interest to examine the effect of gastric operations on gastric function.

The material of the First Surgical Clinic of the University of Budapest covering the years 1914 to 1924 has been recently reviewed and the results have been published elsewhere.[1] In this study the gastric material has been reviewed from the standpoint of functional results after the most frequent types of operations, especially gastrojejunostomy and partial gastrectomy, with incomplete observations on pyloric exclusion.

The operations have been performed by five members of the staff with uniform indications and technique. In the absence of an absolute indication for surgical interference such as perforation, mechanical obstruction of the pylorus or hemorrhage, medical management was advised for six to eight weeks. In case of unsuccessful medical treatment or recurrence of symptoms, surgical interference seemed indicated.

Factors in Ulcer Formation. The etiology of ulcer in the stomach and duodenum is not known. However, as in other fields of human pathology, it seems to be recognized that it is always the coincidence of several factors, of multiple conditions, that produces a definite pathological lesion. The idea of this conditionalism in the etiology of diseases has proved to be very fruitful. In the case of ulcer, two factors are known to play a very important part in the etiology. The one is the mechanical factor. The "Magenstrasse" of Waldeyer, the path where the meals pass daily along the lesser curvature into the duodenum, has been pointed out by Aschoff[2] in the pathology of ulcer.

While acute lesions can appear anywhere in the gastric mucosa, they heal rapidly. Chronic ulcers, however, are found with very few exceptions on this gastric avenue. Two points of predilection are the pylorus and isthmus. This latter is located between corpus ventriculi and vestibulum pyloricum. Careful anatomical study reveals the existence of four longitudinal rugae in the mucosa of the lesser curvature, which exert a special longitudinal traction in the isthmic region. If, then, an acute defect ensues here, the margins are spread apart and are open to the digestive action of gastric juice. The mechanical factors are also responsible for the shape of these ulcers. The cardial margin is undermined and becomes more and more excavated. Perforation occurs generally in a sack formed here, the niche of roentgenologists. The pyloric edge of the ulcer is flattened out, resembles an ascending stairway, ironed out by the passage of food. The longitudinal folds with their traction toward the pylorus, and the rolling action of the food are responsible for site and shape of these isthmic ulcers.

The role of acidity has been recognized in an empirical manner for many years, but has received definite proof from the experimental work of Mann[3] who showed that while it is hardly possible to increase the acid secretion in a constant manner, the same effect could be obtained by lessening the alkalizing secretion, or rather by diverting it to a farther point. With an ingenious operation based on this

assumption, typical chronic ulcers were produced in a high percentage of cases. Von der Hütten,[4] Lim and Dott[5] produced chronic jejunal ulcers at the site of anastomosis by occluding the pylorus and thereby inhibiting regurgitation. This type of operation has also given clinically the highest percentage of jejunal ulcers. Clinical observations have been here long ahead of animal experiments. The two factors: The mechanical and the acid factor, each have an anatomical and experimental basis.

As to the clinical proofs: We know that about 95 per cent of all ulcers develop on or close around the lesser curvature; that is, on the pathway of hot and icy, bulky and unchewed food. We also know that the pyloric exclusion of von Eiselsberg just mentioned above which consists of closing off the stomach completely before the pylorus, followed by gastrojejunostomy has shown the greatest percentage of jejunal ulcers. Haberer reports 20 per cent, Clairmont 28 per cent of jejunal ulcers after this operation. The author himself has abandoned this method which originally had the idea of protecting the ulcer from mechanical injury, but did not consider the acid factor. By excluding the pylorus completely, the physiologic regurgitation of duodenal contents—the alkalizing secretion—was made impossible. The chances for the formation of a new ulcer are great, as it seems that an open or at least partly open pylorus is one of the most important factors in avoiding jejunal ulcer. A stenotic pylorus, allowed to remain, may cause reflex muscular and vascular spasms, as maintained by Haberer.[6]

Own Observations. Gastroenterostomy. In analyzing our functional results obtained by gastrojejunostomy only 50 per cent of the 274 patients obtained complete relief from the operation. In 22 per cent fair results, meaning occasional complaints, and in 28 per cent poor results, meaning recurring of symptoms or appearance of new symptoms, have been observed. We have tried to follow-up all cases with chemical analysis and Roentgen ray examination. Two hundred patients examined before and three weeks after the operation showed on the average that the free hydrochloric acid was lowered from 24 to 23 points, the total acidity from 54 to 46 points. There is then practically no lowering of acidity after the anastomosis. This observation is contrary to many other reports. As a result of the close follow-up with the Roentgen ray, the following types could be made out:

In one type of patient the ulcer healed—this is especially true of the flat duodenal ulcer. There were no spasms and the acidity was not high. The pylorus opened up completely and a condition arose that we see when an unnecessary anastomosis is performed. The proximal jejunal loop fills up and obstructs intermittently the passage to the distant loop. A discomfort ensues, not due any more to the ulcer itself, but to the anastomosis. How disconcerting such conditions may be is best shown by the statistics of Balfour from the Mayo Clinic who reports 131 unnecessary anastomoses

that had to be disconnected. The anastomoses in these cases were unnecessary probably at the time of the operation, but it is possible that even although an ulcer is present at the time of operation it may disappear and make the operation superfluous. The better the operation works the more is the chance of this condition. As an anastomosis is never performed in our clinic without a definite lesion, this operation was not unnecessary but became unnecessary after the ulcer healed.

In another type of case, the pylorus is partially or completely closed by scar tissue. The gastric contents move only through the anastomosis. If the pyloric obstruction is caused by spasm or edema it will subside but a callous scar will never disappear. On the contrary because of disuse it may close down completely. A duodenal regurgitation is impossible. The neutralization is faulty. The same condition appears as in the case of pyloric exclusion and in the experiments of Mann. The chances of jejunal ulcer are great. In our 274 anastomoses 28 per cent had poor functional results. In 18 per cent, a jejunal ulcer could be demonstrated. Unfortunately, I cannot furnish reliable statistics as to how many of these 18 per cent had a closed pylorus. We have seen jejunal ulcers with open pylorus too, but undoubtedly in the majority of these cases the neutralization was at fault.

Between these two extreme types, namely Type I, where the anastomosis has healed the ulcer and its symptoms completely and has become unnecessary, and Type II, where a jejunal ulcer developed mostly in the presence of complete pyloric obstruction one finds a large number of cases—50 per cent in our statistics—where pyloric spasm has been relieved, the pylorus, though the meals pass through the anastomosis, is patent and Nature has adapted herself to this new mechanism. But how often and how easily is this mechanism upset by a mistake in diet, a mental strain or an intercurrent disease.

A patient with anastomosis so far as general experience goes has to observe certain restrictions in diet for several years and this is one reason for the great difference in American and European statistics. The charity material of the University Hospital in Europe will not and cannot keep a diet. Besides, a patient may have dieted before an operation and when taking the risks of surgical interference wishes to be relieved once and for all. Also financial consideration plays a great part. Charity hospitals in this country have surely made the same observation. On the other hand, private hospitals can more readily insist on a longer diet and the diet is observed rigidly. The low percentages of 1 to 2 per cent of jejunal ulcers reported in this country may be partly due to this factor. The eradication of all foci of infection is perhaps done more systematically but it is very difficult to determine its ultimate value.

Results with Partial Gastrectomy. In our gastric resections the relief from acidity has played a conspicuous part. In 200 patients

chemical analysis has been carried out before and three weeks after the operation. The free hydrochloric acidity was lowered in the average from 30 points to 2 points, the total acidity from 56 points to 15 points. Table I compares these results with those obtained after anastomosis. While these figures do not claim to represent absolute values, their comparative value is important. All analyses have been carried out three quarters of an hour after an Ewald breakfast. As to the motility the spasms are naturally gone. The gastric stump which should be about one-third of the stomach increases its capacity in time. Four to five months after operation, on the average, the barium meal is retained for three to four hours, and three meals a day can be taken. A cause for longer retention of meal in a blind atonic pouch has been eliminated by a technical modification.[1]

TABLE I.—LOWERING OF GASTRIC ACIDITY.

Type of operation.	Number of cases.	Average acidity.	
		Before operation.	After operation.
Gastrojejunostomy	200	F.HCl. 24 T.A. 53	F.HCl. 23 T.A. 46
Partial gastrectomy	200	F.HCl. 30 T.A. 56	F.HCl. 3 T.A. 15

F.HCl. = free hydrochloric acid; T.A. = total acidity.

TABLE II.—MORTALITY AND LATE RESULTS AFTER ANASTOMOSIS AND RESECTION (FIRST SURGICAL CLINIC, UNIVERSITY OF BUDAPEST).

Type of operation	Number of cases.	Mortality (per cent).	Late results (per cent).		
			Good.	Fair.	Poor.
Gastrojejunostomy	274	5.8	50	22	28
Partial gastrectomy	226	5.4	84	10	6
Secondary resection:					
For recurrence	20	7.3	81	14	5
For jejunal ulcer	21				

Classification of results: Good = no complaints; Fair = occasional complaint; Poor = return of symptoms or new symptoms.

First 200 anastomosis . . . . . 2.7 per cent mortality
Last 74 anastomosis . . . . . 7.7 per cent mortality
Last 88 resections . . . . . 3.3 per cent mortality

The question arises how these patients without pylorus, antrum and free hydrochloric acid are going to fare in life. Six years have elapsed since the first resections. The time of observation is not long enough to allow conclusions. Up to the present time no intestinal disturbance and not one case of pernicious anemia has been observed. On some patients, blood examinations have revealed no suggestion of primary anemia. The functional results were much better than in the anastomosis group. Table II gives comparative results after these two types of operation. The mortality figures show a variation, following a change in indication and

technique. The high mortality of the last 74 cases of anastomosis is due to the fact that more recently this operation was only performed when resection was not possible either because of the extent of the lesion or because of the general bad state of the patient. In other words, only bad risks were submitted to this type of operation. On the other hand owing to the constantly growing experience, the extensive use of local anesthesia, the use of Hueltls' intestinal sewing machine and to a modification of Finsterer's technique, the mortality of resections was brought down to 3.3 per cent in the last 88 cases. The comparable figures are therefore 2.7 per cent for anastomosis and 3.3 per cent for resection.

The high mortality of secondary resections, namely, 7.7 per cent, that increases up to 20 per cent in gastrojejunocolic fistulas, as has been reported quite recently from the Mayo Clinic,[7] ought to be added to the mortality of anastomosis. This is justified on account of the fact that in all secondary resections an anastomosis has been previously done. In our series, not one jejunal ulcer has been observed after gastrectomy although a few of such cases have been published.

The mortality of resections, then, compares favorably with those of the anastomosis. The danger of malignancy on the basis of ulcer is eliminated. In our series 25 per cent of gastric ulcers showed histologic evidence of cancer. Perforation and hemorrhage of the ulcer that may both occur after an anastomosis is impossible. Although being called a mutilating, destructive operation, the functional results are better in gastrectomy than in anastomosis. This latter upsets the normal function of the stomach considerably, whereas with resection the acidity is controlled; the spasms are relieved, the loss of two-thirds of the capacity is compensated and the normal grade of retention obtained.

Other types of gastric operation were not followed up routinely with chemical analysis and Roentgen ray, this study being intended as a comparison between gastric and partial gastrectomy. Out of 85 cases of pyloric exclusion, 30 per cent showed poor results. In 21 per cent jejunal ulcers could be demonstrated, thus confirming the results of Haberer and Clairmont. Nothing could prove better the importance of neutralization, so forcibly emphasized by Mann. In various types of excision, such as cuneiform, longitudinal and sleeve resection, the danger of jejunal ulcer is eliminated. In our 41 cases, however, 20 per cent had poor results. In 6 per cent recurrent ulcers could be demonstrated, in 5 per cent symptoms of stenosis occurred. No pyloric or duodenal ulcers were excised, although this may be the method of choice in selected cases.

In this series of 676 gastric operations no distinction has been made between gastric and duodenal ulcers. It is well felt, that the pathology of these two types would deserve a separate consideration. Gastric ulcer is resistant to medical treatment, it penetrates readily and may undergo malignant degeneration; duodenal ulcer

may heal by medical treatment, heals very frequently by itself, is often superficial and never becomes carcinomatous. Yet in order to evaluate the relative merits of gastrojejunostomy and gastrectomy, and because of the unquestionable effect of lowering the acidity and removing the lesser curvature as important factors, gastrectomies have been performed for gastric and duodenal ulcers alike.

Summary. This short review is presented to prove that gastric resection for ulcer, done in a satisfactory number of cases with equal indications for operation, compares favorably with anastomosis. Further experience will help to establish more concisely the indications for the two operations. From a physiologic point of view, anastomosis, although a smaller surgical interference, does not offer any advantages. The perverted physiology of the stomach which follows this operation may have worse consequences than the original lesion.

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THE TREATMENT OF AFRICAN SLEEPING SICKNESS WITH TRYPARSAMIDE ADMINISTERED INTRAMUSCULARLY.

By Judson C. King, M.D.,
SONA BATA, BELGIAN CONGO.

(From the American Baptist Foreign Mission Society Hospital, Banza Manteke, Belgian Congo.)

The purpose of this paper is to report the results of the treatment of 24 cases of human trypanosomiasis with tryparsamide administered intramuscularly. The cases were treated at the American Baptist Foreign Mission Society Hospital at Banza Manteke, near Boma and Matadi, in the Belgian Congo, in which district sleeping sickness is endemic.

When working under hospital or field conditions that demand the employment of the poorly trained native, it is often far easier to employ the intramuscular than the intravenous mode of drug administration. In the great majority of patients treated with tryparsamide, as reported by various workers,[1-9] the drug has been

given intravenously and its therapeutic action by this route has been amply demonstrated. Pearce[1] treated 4 patients with single intramuscular injections of the drug, and thought that the effects were more pronounced and endured somewhat longer than after intravenous injection. The cases so treated were early ones showing normal or only slightly increased cell counts of the cerebrospinal fluid. It was of interest, therefore, to study the effect of tryparsamide injected intramuscularly, particularly in patients in the more advanced stages of the disease, paying especial attention to the general clinical results obtained and to the changes taking place in the cerebrospinal fluid, the blood and the lymph glands.

Type of Patient and Source of Infection. From more than 500 cases of trypanosomiasis under my care, 24 patients, both male and female, were chosen for this study. These patients may be classified as follows: (1) Early stages of the disease with no previous treatment; (2) later stages of the disease with no previous treatment; (3) later stages of the disease with previous treatment, that is, with antimony, atoxyl, or a combination of the two.

In the great majority of the cases the disease was well advanced and definite clinical symptoms of nervous involvement were present; some of the patients were not able to stand or sit and were awakened only when forcefully disturbed. All were more or less liable to the bite of the tse-tse fly throughout treatment, as most of them after the first two or three treatments walked to and from their villages each week.

As the Glossina palpalis is the only observed carrier in this district and Trypanosoma gambiense the only trypanosome known to be responsible for human trypanosomiasis in this section of Africa, there can be little doubt as to nature or means of infection.

Conduct of Investigation. Each patient was examined before treatment was begun, the weight, temperature, pulse rate and general symptoms being recorded. In addition, the following microscopic examinations for trypanosomes were made: (1) Of juice aspirated from cervical lymph glands; (2) of the sediment obtained by centrifuging 10 cc. of blood, employing the triple centrifugalization method described by Broden;[10] (3) of the cerebrospinal fluid. The cell content of the cerebrospinal fluid was also estimated. One cross-ruled field (1 mm. sq.) in the usual Thoma-Zeiss chamber was counted.

Administration of Tryparsamide.* Tryparsamide is the sodium salt of N-phenylglycineamid-*p*-arsonic acid; the drug is easily soluble and no difficulty is experienced in obtaining a clear solution in boiled rain water. Solutions of 20 per cent and 30 per cent were employed, and injections were made into the gluteal muscles.

* The author wishes at once to express his appreciation and gratitude for the kindness of the Rockefeller Institute in making possible these experiments by the liberal supply of tryparsamide placed his disposal and, also, for the encouragement and help given by Dr. Louise Pearce of the Institute.

One or two series of treatments were given, each series consisting of ten weekly doses. A 3-gm. dose was employed for the patient of approximately 50 to 60 kilos, a smaller dose being given in the case of smaller individuals and of children.

Results. The essential features of the laboratory and clinical observations of these patients are stated in the accompanying tables. For convenience, a division has been made of those patients who had had no previous treatment and those who had been previously treated with atoxyl or antimony or both.

In Tables I and II are recorded the summary of the treatment and the changes which occurred in the cerebrospinal fluid, as indicating in a striking manner the effect induced by tryparsamide in these two groups of patients. Mention is also made of the trypanocidal effect of the drug as determined by the microscopic examination of the lymph gland juice and centrifuged blood, while the last column in the tables gives the two periods of time during which each patient was observed, the first dating from the beginning of drug administration and the second from the last dose given.

Brief clinical notes made at the time of admission and a statement of the general physical and mental changes which took place during and following treatment follow the discussion.

Discussion. The beneficial results of tryparsamide administered intramuscularly to this group of patients were pronounced. In the first place, it was found that in both the early or late stages of the disease in patients who had not been treated with other drugs (Table I) single intramuscular doses of 2 or 3 gm. of tryparsamide brought about the disappearance of trypanosomes within five to seven days. This fact was shown by the microscopic examination of lymph gland juice, peripheral blood and the cerebrospinal fluid. Moreover, the cells of the cerebrospinal fluid were reduced in number and the fluid returned to a state approximately or actually normal.

In general, equally favorable effects were noted in patients who had been treated with other drugs prior to the administration of tryparsamide (Table II), as shown by Nos. 1001, 1014, 1023 and 1024. However, in certain patients (Nos. 1006 and 1001) the reduction of the cell content of the cerebrospinal fluid to normal limits was brought about much more slowly, or, as in cases Nos. 1015 and 1016, required a second series of treatments; in the last mentioned 2 patients, it is not certain but that still further treatment may be demanded. In one patient, No. 1017, the response of the cell content of the cerebrospinal fluid to the treatment was limited, the symptoms increased in spite of it, and death occurred. From these few observations we are inclined to believe that chronic cases of African sleeping sickness previously treated with atoxyl and antimony do not react as promptly or as favorably to tryparsamide as those which have not been previously treated with these drugs.

TABLE I.—RESULT OF TRYPARSAMIDE THERAPY IN PREVIOUSLY UNTREATED PATIENTS. INTRAMUSCULAR ADMINISTRATION.

Case No.	Weight (kilos).	Treatment.			Gland puncture.		Centrifuged blood.		Cerebrospinal fluid cells per c.mm.		Duration of nonrelapse.	
		Number and size of dose.	Total amount (grams).	Solution, per cent.	Before treatment.	After first dose.	Before treatment.	After first dose.	Before treatment.	After first dose. (weeks.).	After first dose (weeks).	After last dose (weeks).
1007	63.2	10—3.0	30.0	30	+	−	+	−	339+†	203 (2) 60 (8) 5 (13) 5 (18) 5 (19) 3 (30) 3 (38) 3‡ (49)	49	36
1021	32.3	10—2.0	20.0	20	+	−	+	−	235+†	30 (5) 6 (9) 4 (30) 4‡ (34)	34	25
1011	54.5	11—3.0	33.0	30	++	−	+	−	177+†	71 (6) 10‡ (11) ? (48)	48	37×
1008	44.1	10—3.0	30.0	30	++	−	+	−	155†	54 (4) 15 (10) 2 (15) 3 (20) 3 (29) 3‡ (49)	49	39
1019	47.3	12—2.0	24.0	20	+	−	+	−	198+†	45 (7) 20 (11) 8‡ (20)	20	9
1005	68.2	10—3.0	30.0	30	+	−	+	−	80+†	30 (5) 25 (12) 15 (18) 7 (22) 4‡ (31)	31	19
1012	36.4	10—2.0	20.0	20	+		+		60†	36 (6) 20 (11) § (16) 5 (17) 0 (29) 0 (44)	44	34
1003	50.0	10—3.0	30.0	30	++	−	+	−	34+	10 (5)	49	26

1003	50.0	10—3.0	30.0	30	++	−	+	−	34+	10 (5) 10 (11) 10 (13) 8 (18) 5 (21) 0 (33) 3 (49)	49	38
1002	52.3	10—3.0	30.0	30	+	−	+	?	28+†	25 (5) 10 (10) 10 (14) 5 (19) 5 (21) 3 (33) 0 (48)	48	38
1013	49.5	10—3.0	30.0	30	+	−	+	−	11†	3 (10) 3 (15) 3 (18) 2 (29) 2 (44) 2‡ (47)	47	37
1010	54.7	11—2.0	22.0	20	−		+	−	10	5 (5) 5 (10)	26	15×
1020	43.6	10—2.0	20.0	20	+	−	+	−	100†	57 (5) 15 (9)	9	
1004	20.0	10—1.5	15.0	30	++	−*	+	−*	4	● (5) ● (10) ● (16) ● (21) ● (34) ● (48)	48	38
1022	50.0	11—3.0	33.0	30	+	−	+	−	294+†	38 (4) 20 (11) 20 (16) 20 (26) 10 (32) 10 (36)	48	13×
		One month intermission										
1009	32.7	10—2.0 9—1.5	20.0 13.5	20 30	+	−	+	−	●	● (4) ● (10) § (15) ● (38) ● (44) ● (47)	47	−
		7 months intermission										
		2—2.0‖		30								
		7—3.0‖	25.0	30								

* Examination made after fifth dose.
‡ Normal cell types—in some specimens an occasional large mononuclear.
● Normal cerebrospinal fluid.
† Large mononuclears and mulberry cells present.
‖ Drug administered intravenously.
§ Specimen contaminated by blood.
× Clinical observation only.

TABLE II.—RESULT OF TRYPARSAMIDE THERAPY IN PREVIOUSLY TREATED PATIENTS. INTRAMUSCULAR ADMINISTRATION.

Case No.	Weight (kilos).	Treatment.			Gland puncture.		Centrifuged blood.		Cerebrospinal fluid cells per c.mm.		Duration of nonrelapse.	
		Number and size of dose.	Total amount (grams).	Solution per cent.	Before treatment.	After first dose.	Before treatment.	After first dose.	Before treatment.	After first dose (weeks.).	After first dose (weeks).	After first dose (weeks).
1001	63.2	10—3.0	30	30	+	−	+	−	250+†	57 (6) 30 (17) § (22) 23 (23) 15 (35) 10 (50) 10‡ (53)	53	43
1024	21.8	1—2.0 9—2.0	20	30 20	+	−	+	−	143+†	75 (5) 20 (10) § (20) 5‡ (26)	26	16
1006	63.6	10—3.0	30	30	+	−	+	−	69	45 (9) 35 (13) 30 (36) § (50)	50	37×
1023	39.1	10—2.0	20	20	−		−		35†	10 (5) 6 (10) 2‡ (16)	16	6
1014	50.9	10—3.0	30	30	+	−	+	−	9	4 (12) 3 (17) 3 (24) 3 (30) 2‡ (45)	47	35
1018	46.8	8—2.0 Atoxyl	16	20	−		−		260+†	Refused	37	30
1015	38.2	9—2.0	18	20	+	−	+	−	250+†	145 (4) 95 (8) 421 (17) 30 (23) 15‡ (27)	27	
		Nine weeks intermission										
		9—3.0‖	27	30								
1017	40.9	11—2.0	22	20	−		−		90	60 (9) 120 (14) 90 (19) 75 (22) 60 (27)		
		Four weeks intermission										
		5—2.0‖		20								
		4—3.0‖		30								
		5—4.0‖	42	40								
1016	34.1	10—2.0	20	20	−		−		90	55 (7) § (9)	Died Relapse during treatment which is being continued	
		Twelve weeks intermission										
		5—2.0		20						60 (21) 40 (29)		
		4—3.0‖	22	30						240+(35)		

† Large mononuclears and mulberry cells present.
§ Specimen contaminated by blood.
‡ Normal cell types—in some specimens an occasional large mononuclear.
‖ Drug administered intravenously.
× Clinical observation only.

Two patients, Nos. 1014 and 1022, complained of dimness of vision after the second and third dose of tryparsamide. The first patient had formerly received atoxyl while the second had had no previous treatment. Both patients were clinically well-marked examples of the advanced stage of sleeping sickness, and presented symptoms of somnolence, marked tremor and pronounced weakness. Patient No. 1014 had previously been treated with atoxyl but trypanosomes were found in both lymph gland juice and blood; the cell content of the cerebrospinal fluid, however, was almost normal. Patient No. 1022 was a hitherto untreated case; organisms were present in lymph gland juice, blood and cerebrospinal fluid, and the number of cells in the cerebrospinal fluid was greatly increased. No interruption of the treatment of either patient was made on account of the visual disturbance and the symptoms gradually ameliorated with a return to what appeared to be normal vision. The author has noted a similar dimming of vision in other patients under treatment with tryparsamide and more noticeably so in cases previously treated with atoxyl. No serious results, however, have been observed and it would seem that no optic atrophy or injurious drug effect attributable to tryparsamide has occurred.

Certain local effects of the intramuscular administration of tryparsamide were noticed. Induration of the injected area was frequent and in 5 of the cases in which a 30 per cent solution of the drug was employed this progressed to abscess formation. In no instance, however, did this occur with the use of a 20 per cent solution.

In regard to the physical condition of the patients, there was, in general, a striking improvement in weight, strength and mental acuity with a return to what appeared to be a normal state. The nervous symptoms disappeared slowly but consistently and the attitude of the patient became very hopeful and cheery.

There was 1 death in the series. This patient (No. 1017, Table II and Appendix II), a boy, aged twelve years, had previously been treated with two courses of atoxyl without effect on the course of the disease. Although treatment with tryparsamide was followed by a marked amelioration of symptoms and some reduction of the cell content of the cerebrospinal fluid, this improvement was not maintained and death occurred during the second course of treatment.

One relapse occurred during treatment (No. 1016, Table II and Appendix II). This patient, a boy aged fifteen years, had previously been treated with atoxyl, but on admission presented symptoms, including somnolence, of the advanced disease. The relapse occurred during the second course of treatment which was given twelve weeks after the first. It should be pointed out in this connection that although a remarkable clinical improvement to a practically normal state was brought about by the first course of tryparsamide (10 doses of 2 gm.), the cell content of the cerebrospinal fluid was still high at the end of this course.

× Clinical observation only.
‖ Drug administered intravenously.
† Large mononuclears and mulberry cells present.
§ Specimen contaminated by blood.

Attention should be directed to the unusually low cell content of the cerebrospinal fluid in several patients, some of whom presented characteristic symptoms indicating involvement of the central nervous system. Among previously untreated patients with such symptoms Nos. 1003 and 1002 had counts of only 34 and 28 cells per c.mm. respectively, but in both fluids trypanosomes were found. No. 1013, presenting tremor, had a fluid containing large mononuclear and mulberry cells, but a count of only 11 cells per c.mm.; No. 1014 also showed tremors but only 4 cells per c.mm.

The case of No. 1009 is especially interesting: On admission this child presented the symptoms of tremor, lethargy and somnolence, but the cerebrospinal fluid was normal and continued to be so during the total period of observation. Seven months after the first course of treatment there was a return of the tremor and lethargy, which was again entirely relieved by a second course of tryparsamide. Two previously treated patients, Nos. 1023 and 1014, presented similar findings, namely, 35 and 9 cells per c.mm. respectively in the cerebrospinal fluid; they also showed tremors and somnolence. It is noteworthy that the tryparsamide treatment yielded, in each instance, a reduction or holding of the cell count of the cerebrospinal fluid to normal limits and induced amelioration of symptoms during the period of observation.

Finally, it may be said that while no claim of an ultimate cure of these patients is made, no relapse has been observed in 21 of the 23 patients treated.* Eleven patients have been followed for one year, 3 for nine months, 2 for six and seven months, and 5 for four months since admission.

Summary of Case Histories. *I. Patients treated with tryparsamide administered intramuscularly; no previous treatment.*

No. 1007.—M., male, aged twenty-five years. Very advanced case with mental torpor, cephalalgia, tremor, weakness and somnolence. Marked improvement after the first dose and apparently well at the end of course with a gain of 3.1 kilos. Returned to work. Under observation for thirty-six weeks since treatment. No relapse.

No. 1021.—M., male, aged thirteen years. Very advanced case with pronounced tremor, mental symptoms and somnolent periods. Marked improvement in three weeks and in good condition by the end of course with a gain of 2.1 kilos. Under observation for twenty-five weeks since treatment. In continued excellent condition. No relapse.

No. 1011.—M., female, aged forty years. Very advanced case with marked tremor and constant somnolence; had to be carried to hospital. Abscess at site of injection after fifth dose. Marked

* Patient No. 1018 is excluded because of his transference to atoxyl treatment. Patient No. 1017 died, and patient No. 1016 relapsed during treatment which is being continued.

improvement within four weeks and apparently normal by the end of treatment. Gained 2.2 kilos. Returned to work. In excellent condition with no clinical relapse during observation of thirty-seven weeks following treatment.

No. 1008.—K. S., female, aged twenty years. Advanced case with tremor, somnolence, spasticity, cephalalgia and weakness. Marked improvement within three weeks and apparently normal within six weeks. Gain of 4.9 kilos. Returned to work. Continued excellent condition with no relapse during observation period of thirty-nine weeks following treatment.

No. 1019.—M., female, aged thirty years. Advanced case with somnolence, cephalalgia, mental torpor, tremor, pain in extremities and weakness. Marked improvement within two weeks and apparently normal by the sixth week. Gain of 1.4 kilos. No relapse and in continued excellent condition during observation period of nine weeks following treatment. Slight residual increased cell count of cerebrospinal fluid.

No. 1005.—T. L., male, aged thirty years. Advanced case with cephalagia, digital tremor and weakness; sleeping. Abscess at site of injection after fourth dose. Marked improvement after the first dose and apparently normal within six weeks. Gain of 2.7 kilos. In continued excellent physical condition during observation period of nineteen weeks following treatment. No relapse.

No. 1012.—T., female, aged thirteen years. Advanced case with somnolence, lethargy, weakness and slight tremor. Marked improvement within three weeks and apparently normal by the end of treatment. Gain of 7 kilos. In continued excellent condition. No relapse during observation period of thirty-four weeks following treatment.

No. 1003.—T. K., female, aged twenty-five years. Advanced case with somnolence, tremor, hyperesthesia and debility. Abscess at site of injection after sixth dose. Marked improvement within two weeks and in excellent condition within five weeks. Gain of 4.1 kilos. No relapse during observation period of thirty-eight weeks following treatment. Pregnant at time of last observation.

No. 1002.—J. M., male, aged seventeen years. Advanced case with somnolence, tremor, irregular fever, weakness and a dry skin rash. Marked improvement within two weeks and apparently well within five weeks. Returned to work. In splendid condition by the end of treatment which continued during observation period of thirty-eight weeks following treatment. Gain of 4.1 kilos. No relapse.

No. 1013.—M. N., female, aged thirty-five years. Early advanced case with irregular fever, pains in extremities, tremor and weakness. Returned to work four weeks after admission and apparently normal by the fifth week. No gain in weight. Condition continued to be excellent. No relapse during observation period of thirty-seven weeks after treatment.

No. 1010.—N., male, aged eighteen years. Early advanced case with general hyperesthesia, irregular pulse and periodic prostration. Marked improvement within two weeks and no signs or symptoms by the end of course. No gain in weight. In excellent condition and engaged in work fifteen weeks after treatment. No clinical relapse.

No. 1020.—M., female, aged twenty-five years. Advanced case with somnolence, mental torpor, tremor and weakness. Marked improvement within four weeks and in excellent condition by the end of treatment. Returned to work. No further observation. Slight residual increased cell count of cerebrospinal fluid.

No. 1004.—M., female, aged ten years. Early advanced case with irregular fever, pain in extremities, tremor, debility and beginning drowsiness. Abscess at site of injection after sixth dose. Improvement after first dose and apparently normal within four weeks. In continued excellent physical condition with no relapse during observation period of thirty-eight weeks after treatment. Gain in weight during the year was only 1.4 kilos.

No. 1022.—K., male, aged thirty-five years. Very advanced case, almost moribund with marked tremor, somnolence, spasticity and pronounced weakness so marked as to prevent walking. Marked general improvement within three weeks and in good physical condition by eleventh week. After third dose complained of visual dimness which gradually disappeared. Gained 2.2 kilos. Returned to work. Second course given because of continued slight increase in cells of cerebrospinal fluid (20 per cubic millimeter). Continued excellent physical condition. No clinical relapse thirteen weeks after last treatment.

No. 1009.—N., female, aged ten years. Early advanced case with fever, tremor, lethargy; sleeping; normal cerebrospinal fluid. Improvement after the first dose and in excellent condition by the end of the first course. Second course given because of a return of lethargy and tremor although no trypanosomes were found and cerebrospinal fluid was still normal. Marked improvement and apparently normal within six weeks. Total gain of 3.6 kilos. No relapse during total observation period of forty-seven weeks. No observation available after end of treatment.

II. Patients treated with tryparsamide administered intramuscularly; previously treated with atoxyl.

No. 1001.—K., male, aged thirty-five years. Very advanced case with symptoms of somnolence, mental torpor, marked tremor and so weak that he could not stand erect. Marked improvement within two weeks; returned to work in eight weeks and at the end of treatment seemed normal. Gain of 2.7 kilos. No relapse during observation period of forty-three weeks following treatment. A residual increased cell content of cerebrospinal fluid—10 per cubic millimeter.

No. 1024.—D., female, aged eight years. Advanced case previously treated with twelve doses of atoxyl. Symptoms of somnolence, marked tremor and hyperesthesia. Marked improvement within three weeks and in excellent condition in seven weeks. Gained 1.4 kilos during treatment. Continued excellent condition and no relapse during an observation period of sixteen weeks following treatment.

No. 1006.—M., male, aged twenty years. Chronic advanced case with symptoms of somnolence, spasticity, marked tremor and weakness. Improvement noted after the first dose which steadily increased so that by the eighth week patient returned to work. At the end of the course patient appeared normal except for some increase in cells in the cerebrospinal fluid. Gain of 4.9 kilos. No clinical relapse for observation period of thirty-seven weeks following treatment.

No. 1023.—T., male, aged nineteen years. Chronic advanced case with symptoms of somnolence, mental torpor and weakness. Immediate symptomatic improvement which continued and patient returned to work within six weeks. At the end of the course patient was in splendid condition, had gained 2.2 kilos, cerebrospinal fluid was almost normal and six weeks later it became so. No relapse during observation period of six weeks following treatment.

No. 1014.—M., male, aged twenty-eight years. Chronic advanced case with symptoms of somnolence, marked tremor, cephalalgia and weakness. Marked clinical improvement within two weeks and by the end of the course patient was free from any symptoms and his cerebrospinal fluid was normal. Abscess at site of injection after fourth dose. Gain of 2 kilos. Patient complained of dimness of vision after the second dose but this disappeared although treatment was not interrupted. No relapse during the observation period of thirty-five weeks following treatment.

No. 1018.—K. M., female, aged ten years. Chronic very advanced case previously treated with a series of atoxyl injections. Symptoms of somnolence, pronounced tremor, marked hyperesthesia, spasticity and weakness. Definite improvement during the first three weeks and by the end of the fifth week this was marked. At the end of the course patient was symptomless but refused lumbar puncture and was then treated with weekly injections of atoxyl. Thirty weeks after the end of the tryparsamide treatment patient was leading a normal life and free from any symptoms of trypanosomiasis.

No. 1015.—N., female, aged thirty years. Chronic very advanced case with symptoms of somnolence, torpor, spasticity, pronounced tremor, fever and prostration. Marked improvement within two weeks and in excellent condition at the end of the first course; the cell count of the cerebrospinal fluid, however, was 95 per c.mm. A return of symptoms with a rise in the cells of the cerebrospinal fluid to 421 per c.mm. occurred nine weeks after the first course. The

second course brought about a prompt improvement and patient was free of all symptoms and able to return to work after the fourth dose. At the end of this course she was in splendid physical condition; the cell content of the cerebrospinal fluid had fallen to 15 per c.mm. No further observation available.

No. 1017.—J. L., male, aged twelve years. Chronic advanced case previously treated with two series of injections of atoxyl. Symptoms of marked somnolence, pronounced tremor and weakness. Considerable general nervous and mental improvement within four weeks and in much better condition by the end of the first course—was stronger, slept very little and the tremor had almost disappeared. The cell content of the cerebrospinal fluid had been reduced from 90 to 60 cells per c.mm. A second course given because of a return of the symptoms of somnolence and marked weakness; the cell content of the cerebrospinal fluid had increased to 120 per cmm. Patient was only temporarily relieved by the renewed treatment and after nine weeks the symptoms increased markedly and death occurred during sleep four weeks later. (At the beginning of the tryparsamide treatment it was noted that there was a very irregular heart action and at times it was necessary to count the heart beat with a stethoscope. There was also a splenic enlargement and during the second course ascites developed with marked constipation and swelling and bleeding of the gums.)

No. 1016.—D., male, aged fifteen years. Chronic very advanced case with symptoms of somnolence, mental torpor, marked tremor and weakness so that he had to be carried. Considerable improvement within two weeks after beginning treatment and marked improvement within four weeks. In the seventh week the objective symptoms of trypanosomiasis had all disappeared; patient seemed in fine condition and returned to work. The cell content of the cerebrospinal fluid had been reduced from 90 to 55 cells per c.mm. Second course administered because of slight mental torpor together with a feeling of weakness; 60 cells per c.mm. in the cerebrospinal fluid. Immediate improvement up to the seventh dose when there was a return of acute nervous symptoms with a sudden marked increase of cells of the cerebrospinal fluid (240 per c.mm.) and the finding of trypanosomes in the fluid. The last three doses caused some amelioration of symptoms. Treatment being continued. Total gain of 4.9 kilos.

Conclusions. 1. Tryparsamide is well tolerated in 20 per cent solution given intramuscularly, but in 30 per cent solution causes more discomfort and leads sometimes to abscess formation.

2. It has a definite trypanocidal action in the blood, the lymph and cerebrospinal fluid.

3. With the exception of a certain type of previously treated chronic case, tryparsamide, given by the intramuscular route, is a specific in African sleeping sickness incited by Trypanosoma gambiense.

4. Tryparsamide is equally efficacious in all stages of the disease, except in certain cases previously treated with arsenical and antimony preparations in which its efficiency is limited.

5. There is a definite correlation between clinical symptoms, number of cells in cerebrospinal fluid and weekly treatments of tryparsamide, which may be expressed as follows: The number of cells in the cerebrospinal fluid varies inversely and the clinical symptoms improve directly with the number of weekly injections.

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STAPHYLOCOCCUS INFECTION OF THE RENAL PARENCHYMA.

By Paul W. Aschner, M.D., F.A.C.S.,
New York City.

(From the Surgical Services of the Mount Sinai Hospital of New York.)

Staphylococcus infection of the renal parenchyma is of importance to the internist as well as the surgeon and urologist, because its manifestations are so variable, and its clinical onset is often so insidious that the diagnosis is frequently long delayed. In fact, it may be only suspected and exploratory operation may be necessary for final judgment. Thus Marion, recently discussing the subject under the title "On connait mal le phlegmon perinephritique"[1] indicates how poorly acquainted physicians are with the symptoms and diagnosis of this disease.

The more frequent forms of kidney infection, pyelitis and pyelonephritis, present urinary symptoms, abnormal findings in the urine and definite cystoscopic evidence of kidney disease. Culture of the urine in such cases yields Gram-negative bacilli of the colon or related groups in about 80 per cent of cases. In about 20 per cent the staphylococcus or streptococcus is present, at times in pure culture, but more frequently associated with the colon bacillus.

In staphylococcus general infections, miliary abscesses of the kidney are found at autopsy with great regularity, possibly the result of an excretory effort. The cases to be considered here are

not the fulminant sepsis group, nor the pyelonephritis group, but those of localized staphylococcus infection of the renal parenchyma and its coverings, occurring in kidneys free of calculus, hydronephrosis or other known predisposing disorder. Urine examination and culture, roentgenologic and cystoscopic investigation are of almost no assistance in their diagnosis, so that one must depend largely upon the history and the ordinary methods of physical examination. The records of the Mount Sinai Hospital, from 1915 to 1925 include 61 cases of this type.

Etiology. The sex incidence was striking, only 15 females to 46 males. The age incidence showed 8 infants and children, 11 patients above forty years. The majority were between thirteen and thirty years. In 34 cases the history or examination showed a definite focus of infection, a portal of entry, in the form of furuncles, carbuncles, infected fingers, infected wounds, otitis media, or prostatic abscess. One infant had suckled a breast which was abscessed, contracted a stomatitis and then developed a perinephric abscess. The etiologic factor is often not discovered unless specifically and persistently asked for, and a search made for the scars of healed lesions. In many instances, no doubt, the primary focus had been forgotten and its scar overlooked. Eliciting a history of such infection, or finding its scar may be the most important lead in making the diagnosis. The greater frequency of boils and carbuncles in males corresponds with the high relative incidence of this type of kidney infection in men.

Pathology. The process may be regarded, therefore, as a metastatic infection of the kidney cortex. In the usual acute type of case a small abscess develops near the surface of the kidney and rapidly extends or ruptures through the capsule into the true fatty capsule, with formation of a perinephric abscess. By the time the latter is recognized and operated upon, the kidney lesion may have completely healed, or is so covered by granulation tissue and exudate that it cannot be recognized at operation. It is extremely doubtful if primary metastatic infection of the perinephric fat ever occurs.

In less virulent infections, the process may remain localized in the kidney with no breaking down, but with the development of a raised grayish-white area from 2 to 5 cm. in diameter, on section of which small points of yellowish suppuration are discerned. There is usually an associated chronic sclerosing perinephritis. These are the insidious cases of cortical abscess or carbuncle of the kidney.

In other instances a more widespread involvement of the kidney parenchyma, a diffuse suppurative nephritis occurs. Apparently a larger number of cocci enter the renal artery and are scattered to many parts of the kidney cortex. In long-standing or rapidly spreading lesions of this type, purulent infiltration of the medullary pyramids with abscess formation may occur by lymphatic extension or perhaps rupture of abscesses into the tubular system.

The cases forming the basis of this paper are classified as follows:

Perinephric abscess (2 anterenal)	36
Cortical abscess	19
Carbuncle	4
Suppurative nephritis (multiple abscesses)	4

Of the 3 latter groups, 17 were accompanied by perinephric suppuration. In 2 of these the perinephric abscess formed in front of the kidney.

In only 2 cases was the disease proven bilateral. The right side was affected in 26, the left in 33. This is in marked contrast to the bacillary infections of the kidneys which so often affect both organs either simultaneously or in succession.

Clinical Features. Onset. Not a few patients describe a preceding illness which was diagnosed "grippe," that is, malaise, fever, chilliness, sweating, loss of weight. This in some instances had been accompanied by dry cough, and pain over the lower ribs increased by coughing or deep breathing. Often a diagnosis of pleurisy had been made and the chest strapped. The symptoms may, in fact, mark the time of onset of the renal lesion, particularly when the upper pole of the organ is affected and the perinephritis involves the adjacent crus of the diaphragm. These modes of onset may be referred to as the thoracic and influenzal forms. The symptoms, referable to the kidney, may begin while the primary focus of infection is still active, but most often when the lesion is healing or has completely healed. A latent period of several weeks then intervenes. It may be that the cortical abscess of the kidney already exists but gives no sign until perinephritis is set up by its presence.

Another type of onset is the abdominal. Here the first symptoms consist of acute abdominal pain referable to the right or left lower quadrants or to one of the hypochondriac regions, accompanied by nausea and vomiting, followed by fever and leukocytosis. When the pain is referred to the right lower quadrant the diagnosis of acute appendicitis is strongly suggested. In three patients of this series, laparotomy was performed because of a mistaken diagnosis of appendicitis. With right hypochondriac pain gall-bladder disease is suggested. In these cases the process involves the lower pole or the anterior aspect of the kidney and its coverings. The cases with abdominal onset resemble therefore those of aseptic infarction of the kidney, which I have described in another paper[2] and in fact the records include 1 case of perinephritis in a young man with mitral stenosis who recovered spontaneously, and who probably had an aseptic infarct of the kidney. Another group of cases presents a spinal form of onset with spasm of the lumbar and psoas muscles, pain radiating down the thigh, flexion of the hip, interference with the gait, and with the mobility of the spine. They are suspected of Pott's disease and a plaster jacket is sometimes applied on that basis.

The majority have a renal form of onset with acute lumbar pain which may radiate downward along the course of the ureter, at times to the genitalia and thighs. There may be associated frequency of urination, dysuria, or oliguria but these symptoms are too often transient and forgotten. A few cases present marked urinary symptoms at the onset and these usually occur in cases with prostatic infection or abscess, which may be the primary focus not recognized until later in the course of the disease. Infants and young children may present only the general signs of infection until suppuration has fully developed and the mother notes a swelling in the upper abdomen or the lumbar region.

Constitutional Symptoms. These vary with the acuteness and intensity of the infection, and with the extent of the pathologic lesion. In the acute cases the patient is flushed, prostrated, runs an intermittent or remittent febrile course, and the blood shows a fairly high leukocytosis (15,000 to 30,000 leukocytes, 75 to 90 per cent of polymorphonuclears). These patients have either extensive perinephric suppuration, or the kidney itself is diffusely involved. Chills are uncommon, as contrasted with their frequency in the bacillary forms of pyelonephritis, but may occur in the diffuse suppurative type of nephritis caused by the staphylococcus. The cases of cortical abscess or carbuncle without perinephric abscess usually have an insidious course extending over a period of weeks or months. They present a pasty pallor the result of long-standing low-grade infection and absorption. The hemoglobin and erythrocytes are diminished, the leukocytosis is not marked. While they may have a history of a febrile course at the onset, the temperature now ranges around 100°, with only occasional elevations to 101° or 102°. These are the cases most difficult of diagnosis.

Blood cultures were taken in only 17 cases: those which presented constitutional symptoms, or cases in which the fever was unexplained and some type of general infection was suspected. Eleven were made before operation; 7 were negative, 4 showed staphylococci. One of these patients had a small cortical abscess with a large perinephric abscess, another a large perinephric abscess, a third case was complicated by prostatic abscess. The fourth was in the case of an infant with a diffuse suppurative nephritis. The last 2 cases were fatal. Another patient with arthritis, prostatic abscess and cerebral embolism developed bacteriemia shortly before death.

In 6 cases postoperative blood cultures were taken and found negative. In 2 of these the preoperative culture had been positive, and the patients recovered. Two other cases of this group died.

Local Symptoms and Signs. These consist of pain, tenderness, muscular rigidity and spasm, limitation of motion, swelling, palpable mass, edema and redness. They are present in varying degrees and varying combinations according to the location of the lesion in the kidney and the extent of the perinephric involvement.

Lesions of and about the upper pole present little or no rigidity of the lumbar or abdominal muscles, and little or no costovertebral tenderness. There are usually dullness, diminished breathing and râles at the corresponding base of the chest and intercostal tenderness in the axilla. The lung, however, descends with inspiration. Roentgen-ray examination and fluroscopy of the chest are of value in this group, for in 8 cases there was either elevation, diminished mobility or a wavy irregularity of the diaphragm on the affected side. With an increasing amount of perinephric suppuration the lumbar rigidity and tenderness increase, and the kidney becomes palpable as it is pushed downward by the abscess formation. In some instances the kidney remains fixed high up under the diaphragm and a mass is not palpable.

When the kidney lesion is anterior or the exudate lies between the kidney and the peritoneum, the symptoms are referred to the abdomen. There is rigidity of the corresponding rectus muscle, tenderness below the liver edge, or the left subcostal margin, rebound tenderness, reflex gastrointestinal symptoms. A mass may be felt below the liver edge, and may be interpreted as a diseased gall bladder or a high appendiceal abscess. On the left side a neoplasm of the splenic flexure may be suspected; one case of this series was so diagnosed and laparotomy was performed.

When the lower pole of the kidney is involved and the perinephric abscess gravitates downward retroperitoneally, the symptoms are referred forward to the cecal and appendicular region with rigidity of the lower rectus, tenderness at McBurney's point, and rebound tenderness, all of which suggest appendicitis. Three cases were operated upon with this diagnosis. In others, the psoas spasm is so great as to cause flexion contracture of the corresponding hip and Pott's disease of the spine is suspected.

In cases of cortical abscess or carbuncle running a mild insidious course, the kidney may become enlarged and nodular, and there may be so little tenderness that the mass impresses one as a neoplasm involving either the kidney or colon. The mass may move freely with respiration, the kidney and its inflamed atrophic perinephric fat moving within an uninvolved paranephric fatty capsule. Not infrequently colonic inflation or examination with a barium enema is necessary to exclude a tumor of the bowel.

When perinephric suppuration is well developed and an abscess forms between the kidney and the muscles behind it, the most common type of symptoms are present. There is lumbar rigidity and acute costovertebral tenderness, the overlying tissues may be edematous and red. An elastic fluctuating mass is palpated. If the abscess has already perforated through the muscles subcutaneous suppuration is present.

Urinary and Cystoscopic Data. The urine examination in these cases gives little or no clue to the diagnosis. The records of 28

cases show a trace of albumin, a few leukocytes, a few erythrocytes at some time in the course of the patient's sojourn in the hospital. In only 7 cases was pus found in the urine. In the others the findings were negative.

Cystoscopic examination and ureteral catheterization were carried out in 39 cases. In 16, there were changes in function, or in the sediment on the side corresponding to the lesion. In only a few of these were the findings definitely pathologic, such as marked delay and decrease in the indigo-carmine concentration, diminished urea content, and pus in the sediment. The ureteral specimens were cultured in 26 cases. In only 4 did the culture show Staphylococcus aureus on the affected side. In 2 other cases, Staphylococcus albus was grown from the opposite side. The rest were sterile. Of the 4 positive ureteral cultures, 3 were in cases of perinephric abscess and 1 in a case of suppurative nephritis.

Roentgenographic Data. While Roentgen-ray examination seldom gives any positive information in these cases, it is valuable for the exclusion of renal or ureteral calculus, disease of the vertebræ or neoplasm of the colon. The findings on fluoroscopy and Roentgen-ray examination of the diaphragmatic region have already been referred to; they were positive in 8 out of 16 such examinations. In 4 instances the examination of the genitourinary tract showed a large kidney shadow, and in 2 the outlines of an abdominal mass on the affected side. Pyelography was carried out in only a few instances before operation, and in these gave no assistance. Lower and Belcher[3] report a case in which the pyelographic medium was seen to extravasate into the necrotic kidney area.

Diagnosis. The difficulties of differential diagnosis have been indicated in the discussion of the forms of onset. It is of importance to remember that a normal urine, a negative cystoscopic examination, and negative Roentgen-ray findings do not exclude suppuration in the kidney parenchyma. The history of a furuncle, carbuncle, paronychia or some other peripheral infection caused by the staphylococcus should be given as much weight when this disease is suspected as the history of a primary tumor in a patient suspected of metastatic deposits.

Errors in diagnosis, of course, can occur in the opposite direction. Appendicitis occurring in a retroperitoneal appendix[4] which extends upward behind the cecum and ascending colon, the tip at times being in front of the kidney, may simulate perinephric abscess very closely and in several instances the appendix has been removed and the abscess drained through the lumbar incision made for exploration of the kidney. Subhepatic abscess secondary to appendicitis, also simulates the condition and is best approached through the anterior half of the usual kidney incision.[5] In one patient exploration of the right kidney proving negative, a subphrenic abscess of the extraperitoneal variety was subsequently discovered.

The acute cases offer little difficulty because perinephric suppuration occurs early and presents definite physical signs. The cases of attenuated infection may be undiagnosed for many months, as they tend to run a course characterized by spontaneous remissions of fever and symptoms. It is in this group that Dr. Beer[6] has advised the use of staphylococcus vaccine in the hope of activating the focus much as tuberculin is used for diagnosis. This was suggested by the bilateral cases, in which after one side had been operated upon, the lesion on the other side manifested itself clinically, although from the findings at the second operation the lesion of the second kidney seemed as old as that of the first. The absorption following the trauma incidental to the first procedure apparently activated a silent lesion in the second kidney.

Prognosis. That cortical infection of the kidney by the staphylococcus can resolve with spontaneous cure of the patient seems very probable from 5 additional cases. These patients gave a history of preceding boils, followed by lumbar pain (1 bilateral), fever and leukocytosis. Under observation the general signs of infection and the costovertebral tenderness disappeared completely and they were discharged apparently well. Inspection of kidneys removed for carbuncle or suppurative nephritis, moreover, shows small, irregularly stellate, ochre-colored areas representing foci of suppuration that have undergone resorption and fatty degeneration.

There were 9 deaths in this series of 61 cases. A man aged twenty-six years, with a cortical abscess and perinephric suppuration died five days after operation from pulmonary embolism, proven by autopsy. This was the only death in the cases occurring in young adults.

Three children died. One ten weeks of age developed a purulent peritonitis due to the perforation of a cortical abscess on the anterior surface of the kidney, after a perinephric abscess behind the kidney had been drained. One child, aged three years, with a diffuse suppurative nephritis and a persistent bacteriemia after nephrotomy developed metastatic involvement of the sternum, multiple lung abscesses and empyema. Nephrectomy should have been performed. Another boy, aged ten years, developed wound infection and purulent peritonitis subsequent to nephrectomy for a large carbuncle of the kidney.

Three elderly people (fifty-six, fifty-nine and sixty-six years) died. One man with prostatic abscess developed a bacteriemia, and cerebral embolism terminated his illness. Another with prostatic abscess showed at autopsy, in addition to the kidney carbuncle, abscesses of the spleen and liver, the periprostatic veins having become involved. One feeble woman developed a metastatic panophthalmitis and cavernous sinus thrombosis.

Two patients died probably because of poor judgment on the part of the operator. In a patient suspected of having a splenic

flexure neoplasm, the laparotomy wound was closed and lumbar drainage deferred; the anterenal abscess perforated and peritonitis supervened. The other patient was operated upon for supposed appendicitis and the surgeon made the mistake of opening the perinephric abscess through the laparotomy incision; empyema and pericarditis developed.

Thus we find that the disease is most fatal in the young and in the old, that bacteriemia and metastatic lesions are apt to occur particularly in the cases with prostatic suppuration, or extensive suppuration of the kidney, and that lesions in front of the kidney are especially dangerous.

Complications. In patients who recovered the following complications were noted: Pleural effusion, 1; empyema, 2, from which the streptococcus was recovered; cholelithiasis and cholecystitis, 1; metastatic cortical abscess of the femur, 1. A patient who had been operated upon for renal abscess two years before coming under our observation for recurrent pain, showed on pyelography "compression of the pelvis suggesting tumor." In 2 cases (1915 and 1925), many days after nephrectomy, large amounts of urine were discharged from the wound, due to vesicoureteral (bladder) reflux. They healed spontaneously upon establishing catheter drainage of the bladder.

Treatment. Although cortical infection of the kidney may occasionally resolve the indication is for exploration and drainage whenever it is reasonable to suspect its presence. The acute cases with frank perinephric suppuration rarely require more than simple drainage through an intermuscular incision. If the kidney is readily accessible and the causative abscess is found, the opening in the latter should be enlarged with the finger.

When there is little suppuration of the perinephric fat and the kidney lesion itself is the important factor, it is best not only to drain or excise the abscess area but also to decapsulate the organ completely because other foci may thus be uncovered and given free exit. In these cases, a rubber dam is placed both in front and behind the kidney to prevent adhesions from forming before it is deemed safe to let the wound heal. Secondary abscesses can readily be opened if this practice is followed.

If the decapsulation reveals widespread infection of the kidney parenchyma and the septic phenomena are not relieved in a few days by this conservative procedure, the offending organ should be removed. Particularly urgent is this indication if a bacteriemia persists after the first operation.

I believe the error of suturing the operative wounds in these cases has been altogether too common. Absorption and wound infection is thereby encouraged. Secondary closure can always be performed, if necessary, when the tissues are clean and granulating. A constant watch for metastatic foci should be observed during the period of convalescence.

Summary. Staphylococcus infection of the kidney parenchyma is usually metastatic from a boil, carbuncle, paronychia or other peripheral lesion. In the acute cases perinephric suppuration develops early and the diagnosis is relatively easy. In the subacute and chronic cases the clinical manifestations are so variable as to simulate various types of thoracic, abdominal and spinal disease. The absence of striking urinary symptoms and urinary changes, the indeterminate results of cystoscopic and bacteriologic examinations all tend to make the diagnosis of cortical abscess or carbuncle of the kidney a difficult one. It is only by bearing the condition constantly in mind, and by giving proper attention to the search for a preceding peripheral infection by staphylococci that the insidious cases may be recognized. The evaluation of provocative vaccine injections must await a more extended experience with the method.

Some of these infections undoubtedly resolve without frank suppuration. The prognosis with proper surgical therapy in young adults is excellent. In children and in older adults it is a graver affection, particularly if other metastatic lesions or venous involvement occur. Nephrectomy is necessary in few cases, such as those with widespread involvement of the renal parenchyma and persistent bacteriemia.

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HEMORRHAGES, THEIR SIGNIFICANCE AND METHODS OF TREATMENT.*

By C. A. Mills.

CINCINNATI.

(From the Laboratory for Experimental Medicine, Department of Internal Medicine, University of Cincinnati.)

The loss of blood in considerable amounts from the body is about equally disturbing to the patient and to the physician. For the patient there exists a sort of inborn terror of approaching calamity as the escape of "life blood" is being watched. This is more particularly true where the source of the bleeding is concealed, as in pulmonary, renal, gastric or intestinal bleeding. There

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is, furthermore, nothing that engenders in the mind of the patient more respect for, and more confidence in, the ability of the physician than that he promptly and completely stop the hemorrhage. This, together with the fact that hemorrhage is the one condition every physician must handle sooner or later, tends to give the subject a lively interest.

The wide occurrence of free bleeding under the most diverse conditions would at first sight make an attempt at classification of hemorrhages seem hopeless. When one considers the bleeding regularly accompanying the physiologic process of menstruation, the truly hemorrhagic states such as hemophilia and purpura, the hemorrhages occurring in the course of many diseases, such as tuberculosis, typhoid fever and other ulcers of the gastrointestinal tract, and, finally, epistaxis, that so often seems to occur for no reason whatever, then one wonders what it is that governs this loss of blood, and what benefit, if any, is to accrue to the body through such loss. One would like to believe that such a frequent happening should have some physiologic function, rather than that it should be a mere purposeless accident.

It is one purpose of this paper to attempt a classification of hemorrhages which will account for practically all types of bleeding, and to show, so far as possible, the underlying cause for the hemorrhage in each case.

Classification of Hemorrhages. One may well divide hemorrhages of all kinds into three main groups:

Group I. Hemorrhages from Physical Causes.

(*a*) *Accidental Trauma.* External injuries, skull fracture, rupture of an organ (liver, spleen, kidney, etc.), bony fracture with perforation of a vessel, ectopic pregnancy with rupture, epistaxis from injury to nasal mucosa, postpartum bleeding, placenta prævia, etc.

(*b*) *Congestion and Venous Rupture.* Hemorrhoids, esophageal varices, pulmonary hemorrhage in lung congestion from heart disease, menorrhagia in most cases, spontaneous epistaxis, bleeding accompanying many tumor growths, etc.

(*c*) *Arteriosclerosis and Hypertension.* Apoplexy, epistaxis.

(*d*) *Surgical Bleeding.*

Group II. Hemorrhages as a Feature of Other Diseases.

(*a*) *Infectious Conditions of Chronic or Semichronic Character.* Pulmonary hemorrhage in tuberculosis, nasal or intestinal bleeding in typhoid fever, peptic ulcer, epistaxis in such chronic conditions as arthritis, furunculosis, and others.

(*b*) *Malignant Fevers.* Diphtheria, measles, smallpox, influenza, and others, at times.

(*c*) *Anemias.* Pernicious anemia and rapidly progressive secondary anemia.

(*d*) *Leukemias.*

(*e*) *Jaundice.* Due to accumulation of bile salts in the blood.

(*f*) *Metabolic Disturbances.* Scurvy and severe malnutrition.

(*g*) *Tumors.* Particularly carcinoma, in many parts of the body.

GROUP III. HEMORRHAGES IN THE TRULY HEMORRHAGIC DISEASES.

(*a*) *Hemophilia.*

(*b*) *Purpura.* Of the truly thrombopenic type.

(*c*) *Melena Neonatorum.*

One might add a fourth division to include the physiologic bleeding of menstruation. No attempt has been made to mention all instances of bleeding, but only representative ones for each subdivision. It is believed, however, that this classification will cover all instances of bleeding. Some cases, it is true, may fall into two groups. For instance, a hemorrhage that starts from a physical cause, may be sufficiently severe to produce a severe secondary anemia, thereby bringing on a real bleeding tendency, as will be described later. This later bleeding would fall into Group II, with an entirely different reason for its persistence.

Causes of the Occurrence of Hemorrhage. Let us now consider the underlying forces acting to produce the different types of hemorrhage. We will take them up group by group, and we will find that the groups differ sharply from one another. In fact, it was this difference in underlying causes that prompted the above classification.

The characteristic feature of the types of bleeding in group I is that the trouble lies, not in the blood itself, but in physical forces acting upon it or the vessels. Thus, congestion may reach a point at which the vessel must rupture, or an external agency may rupture a vessel directly. In any case, the blood, as it escapes from the vessel, clots normally. The spontaneous cessation of the hemorrhage depends on the relief from the force which initiated the trouble. The blood-clotting mechanism being normal, we will see later (under Treatment) that these types of bleeding are quite easily controlled by proper measures for increasing the blood coagulability.

Group II, on the other hand, is strikingly different from the above group in that here the trouble lies in the blood itself, as a result of infection, malnutrition, anemia or jaundice causing chemical alteration of the blood. Thus, in the infections, particularly typhoid fever, tuberculosis and the malignant fevers and in the anemias, there occurs an excess production of antithrombin which acts as the chief causative factor in these conditions. True, in pulmonary tuberculosis we have the erosion and cavity formation, and in typhoid fever and peptic ulcer there exists the tissue destruction. We have found, however, in these conditions a marked increase in antithrombin in the blood, which, we believe, acts as an important contributing cause for the hemorrhages. In the anemias there is

the additional factor of low fibrinogen and prothrombin content in the blood, decreasing the efficiency of the mechanism to stop bleeding. But even where one bleeds an animal (rabbit for instance), not enough to cause a noticeable anemia or reduction in blood fibrinogen, one still gets an excess production of antithrombin for several hours or days thereafter. It is this antithrombin production which often leads to a diminished coagulability of the blood following hemorrhage, rather than to an increased coagulability as is so often thought. In jaundice where an abnormal amount of bile salts is present in the blood, the coagulability is lessened, and if this amount reaches 0.4 per cent concentration, clotting is entirely inhibited. This is due entirely to the direct chemical action of these salts on the clotting process, but the nature of this chemical action is not well understood. Bile salts in 0.4 per cent concentration will redissolve a clot already formed.

In Group III the tendency to hemorrhage seems to exist independent of any other pathologic condition in the patient. Again, as in Group II, the trouble lies in the blood itself. The two groups are to be differentiated by the apparent independence of the abnormal condition in the body in the former group.

In hemophilia the trouble lies wholly in the thrombin-producing, and thrombin-destroying mechanism. Blood fibrinogen and calcium are normal. Active thrombin or tissue extracts, added to hemophilic blood, clot it just as effectively as they do normal blood. The tissue factors are also normally active, and no excess antithrombin is to be found in the blood. As stated above, the abnormality lies in thrombin production and removal. For instance, cephalin added to such blood or serum is incapable of leading to prothrombin conversion into thrombin, while in normal blood and serum it does this with extreme readiness. Also, in hemophilic blood serum the thrombin disappearing is not reconverted to prothrombin by the antithrombin, but seems to be directly removed from the scene of action.[1] We will mention under "Treatment" a means of remedying this defect for a matter of weeks at a time. It has been stated that the platelets here are qualitatively deficient, but the evidence is not entirely conclusive. Clinically, one finds a prolonged clotting and bleeding time with a normal retractility of the clot and normal platelet count.

Purpura of the true thrombocytopenic type appears to be a clinical entity. The hemorrhagic condition seems to be entirely dependent on the abnormal character of the blood and more particularly of the blood platelets. The other clotting factors have not been found sufficiently altered to account for the condition. The platelets are reduced in number, often very markedly, with the result that the blood clot, as it forms in a wound, does not retract to close the wound, and the blood continues to escape through, or around, the soft jelly-like clot. The clotting time may be normal

or prolonged, but the bleeding time is always prolonged. The source of the trouble has been thought to lie in the spleen, where too active a platelet destruction has been observed.[2] Following splenectomy, the platelet count abruptly rises to normal and the hemorrhagic state disappears. Some cases, after splenectomy, however, have shown a later reduction in the platelets to their former low level, but without the recurrence of bleeding. The real cause of the platelet reduction is, therefore, still uncertain.

The milder forms of purpura, consisting mainly of single attacks lasting from one to three weeks, are usually symptomatic, and the cause is to be sought among the diseases listed under Group II. Occasionally a purpuric attack cannot be so associated, but a single attack that responds well to the treatment indicated later, should never be classed as true thrombopenic purpura. This type of symptomatic purpura is not helped by splenectomy; in fact, it responds so readily to much simpler treatment that such a major operation should never be considered.

Melena neonatorum, although at present classed as a hemorrhagic disease, probably will be found explainable on a physiologic basis in the near future. All infants exhibit a lengthening in their clotting time beginning on about the third day, increasing to the fifth or sixth day, and then returning to normal on the seventh or eighth day.[3] This lengthening in the clotting time is often twofold, or more. A small number of infants show this change to a very marked degree, and develop a dangerous hemorrhagic condition in the blood. It is among this latter group that the cases of bleeding occur. The clotting and bleeding times are prolonged, but so far no study of the blood has brought forth the reason for the alteration. The hemorrhagic cases represent, then, merely an exaggeration of the physiologic change occurring in all infants, and this promises well for a solution of the trouble when properly attacked. Perhaps the most important phase of this delayed coagulation in infants' blood from the third to the eighth day, is its bearing on intracranial hemorrhages. Only too often are infants born under difficulty or with some degree of cyanosis, who are apparently normal for the first day or two, later developing signs of intracranial bleeding and either dying or being left permanently harmed. The reason for this is apparent: difficult or instrumental delivery, or cyanosis from any cause, may lead to the rupture of a small cerebral vessel, which normally would be of no consequence, but when the hemorrhagic state later develops in the blood, this small opening assumes dangerous proportions. We will mention prophylaxis against this contingency later.

Treatment of Hemorrhage. We will first consider the treatment of bleeding in general, and afterward take up in detail instances where special methods should be used.

It is truly remarkable the lack of progress that has been shown

in the last century or so, in the care of a patient with hemorrhage. So very often do we still see the old treatment of bed rest and absolute quiet being prescribed by the physician for internal bleeding, the outcome to be left to Nature. Or if the situation becomes critical the surgeon is called in. The use of the ice bag, bandaging of limbs, and so forth all have their proponents, but their efficacy is ever in doubt. The use of whole blood transfusion was a great step forward, although it was usually used to quicken recovery after the bleeding had ceased. It was thought that the injection of the blood, with the wound still open, would only lead to still worse bleeding. Today we know that transfusion stands as one of our most certain means of arresting hemorrhage of whatever kind. Its technical difficulties, however, render it a reserve emergency measure to use as a last resort.

A second forward step in the control of external bleeding was taken when tissue extracts were brought forward for local application.[4] The brain and lung saline extracts were undoubtedly of great value. But the more severe and troublesome hemorrhages are not those accessible for local treatment, so that this discovery of the action of tissue extracts did not aid in more than a small percentage of the cases. What was needed was an efficient coagulant to be given internally that would exert a general action in all parts of the body. Many products were prepared with this point in view, but one thing prevented their success: It was not believed possible to use the really strong coagulants internally without danger of intravascular clotting taking place, and the weaker ones put forth were too ineffective to produce results. It is one purpose of this paper to show that the strongest coagulant may be given hypodermically or by mouth without any danger of intravascular clotting, but with a marked effect on the clotting time of the blood and the cessation of bleeding.

In our last seven years' work[5] we have isolated the active coagulant from tissue extracts, so that it may be used internally without the toxicity of the crude extracts. We have determined the nature of its action in blood clotting, and finally and most important, we have studied its efficiency in the clinical control of hemorrhages. From these studies we now feel that another long step has been taken in the control of bleeding, namely, the safe use of a strong coagulant internally, producing rapid cessation of bleeding in whatever part of the body it occurs. We even prefer the systemic effect for the control of bleeding that could be reached for local treatment.

This coagulant, tissue fibrinogen, begins to exert its effect about one to one and a half hours after subcutaneous injection. Given orally, when the stomach is empty, and followed by a glass of ice water, it exerts its maximum effect within fifteen minutes, so that this is the better emergency measure. Given by mouth, however, one must remember that it must secure rapid passage through the

stomach, else the acid and pepsin will quickly inactivate it. It is better to turn the patient on the right side to facilitate passage into the duodenum. The duration of the effect is about eight hours, following the subcutaneous injection, and four or five hours, following oral administration. There is ordinarily no overdosage under these conditions. Given intravenously, however, any amount is an overdose and may produce instantaneous death from intravascular clotting.

Tissue fibrinogen fulfills the requirements for a coagulant in practically all the hemorrhages of Group I, and most of those of Group II. Its proper and timely use for bleeding cases, with transfusion to fall back upon if the loss of blood has been too extensive, has robbed hemorrhages of much of their danger and has given us a feeling of comparative safety. Of course, unless the physical cause for the rupture (Group I) is found and relieved, we may expect the bleeding to recur at a later date. Likewise, in the hemorrhages of Group II, so long as the altered blood condition prevails, there may be recurrences, especially in pulmonary tuberculosis. Tissue fibrinogen is as effective, however, at the time of each recurrence as at the initial hemorrhage; or, if one considers a recurrence likely (as in typhoid fever) it may be used as a prophylactic measure. Other instances of its usefulness are: (1) To control bleeding in ruptured tubal pregnancy and allow choice of time for operation; (2) in placenta prævia to control bleeding until the fetus has reached a point where it can be delivered safely; (3) to stop intracranial bleeding and bring about quicker shrinkage of the clot and relief from pressure on the surrounding nervous tissue.

Certain of the bleeding states in Group II require quite different treatment from the above. Severe and rapidly progressive secondary anemia, for instance, is one of the most difficult of the hemorrhagic states to treat. Here there are several factors at work. Not only has the great loss of blood reduced the fibrinogen and prothrombin content of the plasma, but it has called forth an excess production of antithrombin. This is characteristic of protracted bleeding, and is just the opposite of the increased coagulability noticed immediately following bleeding that is promptly stopped. For instance, drawing 5 cc. of blood from a rabbit's heart often causes the clotting time of the rabbit's blood to increase two to four-fold within a few hours, and this condition may last for days. We may overcome this disturbance in the anemic patients by the use of blood coagulants, but we still have to deal with a blood which is too dilute to produce a firm clot, even though the clot may form with fair rapidity. We have found that a great many of these cases with a red cell count below 1,000,000 require a transfusion before the bleeding will cease. Unless we can secure prompt effect from coagulants, we proceed quickly to a transfusion.

Jaundice, particularly of an obstructive type, is another condition

that does not benefit from the administration of blood coagulants. Some have advised the use of calcium chloride intravenously to correct the altered coagulability, but in most cases transfusion remains as the most reliable treatment at hand. If the jaundice is only slight, the response to the tissue coagulant is good. Bile salts, when above 0.4 per cent concentration in the plasma, completely inhibit all clotting.

Of the conditions listed under Group III, *hemophilia* is the most interesting. Many instances of bleeding in these patients respond well to tissue coagulants, but only too often must one resort to transfusion as a final safety measure. Fortunately, we can practically always save these patients in this way, although repeated transfusions are at times necessary. One boy in the Cincinnati General Hospital showed no effect from two transfusions, only to stop bleeding promptly when the third transfusion was given within the same week. There exists now a much simpler and more effective method of treating these unfortunate patients. Vines[6] accidentally discovered that the induction of a local protein reaction in the skin of a hemophiliac caused the bleeding to cease promptly and the clotting time to remain quite normal for several weeks. We have applied this treatment to 5 hemophiliacs with good success, watching their clotting time come down to normal as the local skin reaction developed.[1] One merely needs to sensitize the patient to sheep or hen serum by a subcutaneous injection of about 4 cc., and at the end of seven to ten days inject a few drops intradermally. If a single reaction does not bring the clotting time to normal, it may be repeated at weekly intervals until this end is achieved. It is well for such hemophiliacs to be tested every two or three months to see that they remain sensitive, so that one may have available this mode of treatment in case of future hemorrhage. Study of their blood before and after such treatment shows that the fundamental fault has been corrected. Whereas the conversion of prothrombin to thrombin by cephalin is very deficient beforehand, it is almost normal after the treatment.

Purpura of the truly thrombopenic type is as yet poorly understood. Coagulants seem of little value, and here even transfusion often does not avail. In the last few years splenectomy has seemed to offer immediate relief to these patients. Whether they will lapse back into their former state after a time cannot yet be said. Purpura of the symptomatic type, associated with other disease in the system, responds well to tissue fibrinogen, and should never be subjected to splenectomy.

Bleeding in the new-born is the one condition that, above all others, deserves prophylactic, rather than remedial treatment. Once the bleeding here gets well started, the infant has lost a relatively large amount of blood and the refractive secondary anemia state is present to hinder treatment. In such a case one should at once

give the mother's whole blood into the superior longitudinal sinus of the infant. This measure is almost uniformly successful at once, and it is the only one that is so. Our greatest concern in infants, however, should be with that large number that suffer from intracranial bleeding. This so often comes on two to six days after birth and is so destructive before it is recognized, that we should take all possible steps to prevent it. Recognizing the diminished coagulability in the blood of all infants between the second and seventh days, we should institute measures to correct this in all babies whose delivery was in any fashion difficult or unusual, and especially if instruments were used or cyanosis present. Slight rupture of a vessel intracranially may not be evident after delivery until the second day or later, when the bleeding becomes more free. Proper prophylaxis here might well eradicate one of the greatest causes of infant mortality in the first month of life.

In general, one should always bear in mind that hemorrhage is not a condition to dally with, that the longer it progresses the more difficult will it be to stop. One should proceed to energetic measures at the earliest possible moment. Not only will one avoid the added difficulty of stopping the bleeding tendency brought on by the loss of too much blood, but the recovery of the patient will be hastened just in so far as one conserves his blood.

Significance of Hemorrhages. Ambroise Paré, a French barber-surgeon in 1564, wrote: "M. de Frontaine, Knight of the Order of the King, had a severe continued pestilent fever, accompanied with many inflammatory swellings in sundry parts of the body. He had bleeding at the nose for two days without ceasing, nor could we staunch it; and after this hemorrhage the fever ceased, with much sweating, and by the bye the swellings suppurated, and he was dressed by me and healed by the grace of God."

No doubt repeated instances of recovery from disease after spontaneous hemorrhage caused the development of the custom of the therapeutic bleeding which lasted several centuries. Cupping and venesection were long among the most used therapeutic measures, being gradually abandoned in the latter half of the nineteenth century. Experience along other lines has nearly always shown that any custom or measure which persists for centuries is eventually found to be based on sound principles. Mankind may sometimes be long in discovering these principles, but nevertheless they exist. So with bleeding, whether induced or spontaneous, may there not exist a definite beneficial purpose behind the apparently devitalizing process?

During the influenza epidemic of 1918 it was noticed in some of the camps that the soldiers who contracted influenza and had an early hemorrhage recovered most quickly and completely from the disease. This led to a trial of therapeutic bleeding (200 to 300 cc.)

as early as possible in new cases of the disease, with very good results on shortening its course and severity.

We have noticed in Cincinnati that those typhoid fever patients having an intestinal hemorrhage which is promptly stopped by tissue fibrinogen, usually recover from their fever almost by crisis immediately following the bleeding.

When we consider all these facts, may we not rightly conclude that there is surely a close connection between spontaneous bleeding and the cure of disease through stimulation of the immune mechanism? What we particularly need is some way of estimating this curative or stimulating effect of bleeding so that we may give it an intelligent trial. No doubt many spontaneous hemorrhages are stopped too promptly, or else continue too long, for the optimum beneficial effect. If stopped too soon, the reaction is insufficient, while if continued too long the resulting weakness and anemia defeat the purposes of the procedure.

We are concerned least of all with the bleeding occurring, or induced, merely for relief of congestion or lowering of blood pressure. There physical effects are often valuable, but play little part in a general consideration of hemorrhages.

May we not expect in the near future the discovery of the mechanism by which hemorrhage stimulates our resistance to disease, and see a return to an intelligent use of bleeding as a therapeutic measure?

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THE DIAGNOSTIC VALUE OF COLOR OF THE BLOOD SERUM IN PERNICIOUS ANEMIA.

By Arthur M. Fishberg, M.D.,
NEW YORK CITY.

(From the Medical Division of the Montefiore Hospital.)

Among the striking manifestations of pernicious anemia, there has long been recognized a peculiar yellowish discoloration of the skin, variously characterized as lemon, straw, waxy, or whitish yellow, the last being the term originally applied by Biermer.[1] Usually, the scleræ are not colored, but in exceptional instances they may be very yellow. The yellowish color of the skin is not present in all patients with pernicious anemia and as a rule, though not always, disappears during well marked remission. While occasional slight edema and the strikingly well-retained subcutaneous fat shimmering through the transparent skin are involved in the production of the characteristic skin color of pernicious anemia, the ochrodermia is essentially secondary to a yellowish discoloration of the blood serum. In pernicious anemia the serum is much more highly colored than normally, being golden or golden-brown instead of the normal straw-yellow tint. This increase of serum pigment is an exceedingly constant finding in pernicious anemia, as was pointed out by Naegeli,[2] who observed it in every one of 20 cases. As will be noted in the table below, the pigmentation of the serum was above normal in all our 17 cases of active pernicious anemia.

TABLE I.—SERUM COLOR IN PERNICIOUS ANEMIA.

Number.	Hemoglobin. (per cent).	Serum bilirubin. (units).	Serum color.
1	16	5.4	Golden-brown
2	27	5.2	Brownish
3	15	4.6	Golden-brown
4	35	4.6	Golden-brown
5	22	3.8	Dark brown
6	35	3.4	Golden
7	18	3.2	Dark golden
8	20	3.2	Golden
9	36	2.8	Golden
10	55	2.4	Golden
11	50	2.4	Golden
12	48	2.2	Golden
13	42	1.8	Golden
14	35	1.6	Yellow
15	46	1.0	Yellow
16	45	0.5	Golden
17	30	0.5	Golden

The deeper pigmentation is largely due, as van den Bergh[3] showed, to an increase in the bilirubin content of the serum. The above table shows the bilirubin content (estimated by van den Bergh's

method) of the serum in 17 cases of pernicious anemia in active periods, as well as the serum color and hemoglobin percentage at the time the estimation was carried out. The bilirubin content of the serum is expressed in van den Bergh's bilirubin units, 1 unit representing a concentration of 1 part of bilirubin in 200,000 parts of serum. In our experience the normal bilirubinemia is less than 0.8 units, most often well under 0.5 units. The color of the serum was studied by allowing the blood to clot and examining against a white background after the serum had separated.

It is seen that in 15 of the 17 cases the bilirubin content of the serum was above the normal. Cases 16 and 17, in which the bilirubinemia was well within the normal range, showed, nevertheless, a distinct increase in the pigmentation of the serum. In Case 5, the serum, taken about a day antemortem (the hemoglobin estimation was made some time previously), was of a very dark brown color, though the bilirubin content was only 3.8 units. In general, the pigmentation of the serum in pernicious anemia is greater than would be expected from the increased bilirubin content, considerable though the latter may be. Moreover, the golden color has a tendency to a brownish tinge, which may be very marked in exceptional cases, while in obstructive jaundice the discoloration has a greenish shade when an equal concentration of bilirubin has accumulated in the serum. Evidently, hyperbilirubinemia is not the only factor in the production of the increased pigmentation of the serum in pernicious anemia.

Another pigment concerned is hematin, the very frequent presence of which in the serum of patients with pernicious anemia was demonstrated spectroscopically by Schumm.[4] That hematin causes a brownish discoloration of the serum was shown by Schottmüller[5] in cases of gas bacillus sepsis and ruptured extrauterine gestation. When the serum in pernicious anemia becomes brownish, it would seem that this is largely due to the presence of hematin. While several authors (Syllaba,[6] Brockbank,[7] etc.) have reported the presence of free hemoglobin in the serum in pernicious anemia, Naegeli[8] claims that this finding is always an artefact due to errors in technique causing hemolysis after the blood is drawn. Urobilinogen is often present in the serum of patients with pernicious anemia, but in itself is not a pigment, though according to Naegeli[9] it may cause a greenish fluorescence of the serum after long standing as a result of urobilin formation. Brown, Ames, Warren, and Peabody[10] have recently observed lipochrome in the serum during severe exacerbations of pernicious anemia; it was present in the largest amount postmortem.

Differential Diagnosis of Primary and Secondary Anemia. The constancy of the increase in serum pigmentation in pernicious anemia imparts to this symptom more than academic interest. I have found observation of the serum color a very valuable "bedside aid" in the

often difficult differential diagnosis between pernicious anemia and carcinoma having anemia for its present symptom—the *cancer à forme anémique* of the French. In such cases it is well known that quite often neither the blood picture nor the general symptomatology enables one to decide whether the patient is suffering from primary or secondary anemia. Here, observation of the serum color may offer a solution. If the serum pigmentation is increased, it points to the anemia being pernicious. However, this is by no means absolute, for the heightened color of the serum may be the result of hepatic metastases from an occult carcinoma, in which case the amount of urobilin in the feces becomes especially important as an index of the amount of blood destruction. Roessingh[11] found a considerable increase in the bilirubin content of the serum in 7 of 70 cases of carcinoma; in all these 7, hepatic metastases were present. The increased serum pigmentation of hepatic metastases may be differentiated from that of pernicious anemia by the fact that in the former the serum always gives a prompt van den Bergh reaction (Roessingh), while in pernicious anemia the reaction is delayed. Moreover, the increased pigmentation may not be due to bilirubin, but to the presence of an excess of lipochrome. This is common in diabetes as a result of diet and I have seen it in various conditions (including carcinoma) without any obvious explanation. Use of the van den Bergh reaction will prevent the confusion of pigmentation due to lipochrome with that from bilirubin.

More aid in the differential diagnosis between carcinoma with secondary anemia and pernicious anemia is to be obtained from observation of the serum color when it reveals a pale serum. It was stated above that in active pernicious anemia the serum is more highly colored than normally; I have not met with any exceptions to this rule. So that the presence of a pale serum in an anemic patient demonstrates that the anemia is not pernicious but is a secondary anemia (I have not had an opportunity to observe the serum color in the so-called aplastic anemia and therefore am not acquainted with the serum pigmentation in this rare condition). The pale serum may be the only feature that speaks definitely against a diagnosis of pernicious anemia. This was recently strikingly illustrated in 2 cases of profound anemia with combined sclerosis and anacidity, both of which were first considered as pernicious anemia but the blood serum was almost colorless. Each ultimately proved to have a carcinoma of the stomach.

Summary. 1. In the active periods of pernicious anemia the blood serum is more highly pigmented than normally, being golden, golden-brown, or rarely even dark brown. This is due to an increase in the bilirubin content and to the presence of hematin.

2. In an anemic patient the presence of pale blood serum speaks definitely against the diagnosis of pernicious anemia. Observation of the serum color is of particular value in the differential diagnosis between secondary anemia due to carcinoma and pernicious anemia.

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DIAGNOSTIC VALUE OF THE KOTTMANN REACTION IN THYROID DYSFUNCTIONS.

By Ichiro Katayama, M.D.,
NEW YORK.

(From the Department of the Laboratories, New York Post-Graduate Medical School and Hospital.)

About six years ago Kottmann[1] described a colloidal phenomenon produced by mixing blood serum and silver iodid in cases of thyroid dysfunction as a test which gave promise of some diagnostic value. The publication of this report has aroused considerable interest, and in the literature of this country several papers have appeared bearing upon its practical application. Petersen, Levinson, H'Doubler and Laibe[2] have applied this reaction in the study of 70 cases of evident hyperthyroidism, in 65 of which the reaction was delayed in a typical manner. On the 139 controls a normal reaction was obtained in all but 3, and in these it was slightly retarded. The authors concluded that this simple photochemical test was a close index of thyroid activity, and should be of material aid in the clinical and experimental study of thyroid problems. Lyttle and Sutton[3] report observations on the application of this test to a series of 106 children. Of 28 cases with miscellaneous disease, 21 gave normal reactions and 3 retarded. Of these 3 the retardation in 2 could be explained by previous medication. Of the 33 cases of acute infections, accelerated reactions were obtained

in 15, retarded in 5 and normal in 13. In cardiac cases an acceleration was usually obtained. Kramer[4] has compared the Kottmann reaction with basal metabolic rates, and from his observations concludes that the Kottmann reaction can be said to be of value in measuring the degree of thyroid secretion.

The manner of performing the test is described as follows: To 1 cc. of clear serum 0.25 cc. of 0.5 per cent potassium iodide, and 0.3 cc. of 0.5 per cent silver nitrate solution are added. This produces a suspension of silver iodid in the serum, and this suspension is exposed for five minutes to a 500-Watt Mazda lamp at a distance of 25 cm. Then 0.5 cc. of 0.25 per cent solution of hydroquinon are added and the color changes are observed at five-minute intervals. In the normal reaction a brown color due to partial separation of the free silver from the iodid makes its appearance promptly. The color changes vary from a light yellow to a dark brown. The method of interpreting the reaction can be described best by reference to Chart I. A normal reaction is indicated by the appearance of a faint yellow color in the first two and a half minutes, a light brown in five minutes and a dark brown in ten or fifteen minutes. If the dark-brown color appears at the end of the two-and-a-half- or five-minute interval the reaction is considered accelerated. However, when the dark-brown color does not appear before the twenty-minute interval the reaction is slightly retarded (+); if not before the twenty-five-minute interval, retarded (++); not before the thirty or forty minutes, markedly retarded (+++); not before sixty minutes, strongly retarded (++++).

CHART I.—EXPLANATORY CHART—KOTTMANN REACTION.

2½ min.	5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	40 min.	60 min.	120 min.	Remarks.
L	D	D								(−)
D	D	D								Accelerated
O	L	L	D	D						(0)
F	L	D	D	D						Normal
O	O	F	L	D	D					(+)
O	F	L	L	D	D					Slightly retarded
O	O	F	L	L	D	D				(++)
O	F	L	L	L	D	D				Retarded
O	O	O	F	L	L	L	D	D		(+++)
O	O	F	F	L	L	D	D	D		Markedly retarded
O	O	O	O	O	O	F	F	L	L	(++++)
O	O	O	F	F	L	L	L	D	D	Strongly retarded

O = No color change
F = Faint yellow brown
L = Light brown
D = Dark brown

Petersen and his coworkers and Kramer give an excellent discussion of the physicochemical basis of the reaction. It is not necessary here to explain the underlying principles of the test

beyond the statement that the retardation of the reaction is due to the presence in the blood serum of a colloid which protects the colloidal-silver iodid. In the presence of this protective colloid the silver iodid is maintained in the form of a suspension of fine particles. When this suspension is exposed to light and the hydroquinon is added, the reduction to free silver proceeds at a rate inversely proportional to the fineness of the particles. In the absence of this protective colloid from the serum, or when its concentration is diminished coarser particles of silver iodid are formed, and a more rapid reduction to free silver occurs after exposure to light and the addition of the hydroquinon. An increase in thyroid secretion increases the concentration of this protective colloid in the blood serum, and a diminished thyroid secretion decreases its concentration. Hence the reduction from silver iodid to silver will be most rapid in hypothyroidism, least rapid in hyperthyroidism and normal thyroid function will produce a mean between these two.

The present communication presents the results obtained in comparative studies of glucose tolerance, basal metabolism and the Kottmann reaction in 101 cases, including hyperthyroidism and various pathologic conditions. The procedure adopted in these studies was to have the patient report at the respiration laboratory in the morning after a fourteen to fifteen-hour fast for the determination of the basal metabolism. I am indebted to Dr. C. V. Bailey for the privilege of using the data relating to basal metabolism. Following the basal-metabolism test the glucose tolerance was determined according to the method described by Killian.[5] The control specimen of blood was used for the Kottmann reaction and for a general chemical analysis.

The results of these studies obtained on 21 cases with clinical evidence of dysfunction of the thyroid gland will be given first. In these the basal metabolic rates vary from 4 per cent below to 86 per cent above the average normal. According to the criteria specified by Killian, all of these subjects with the exception of Cases 2 and 13 show a lowered tolerance for glucose. The ingestion of the glucose (1.75 gm. per kilogram in 50 per cent solution by mouth) has produced a more or less persistent hyperglycemia and glycosuria. In Cases 2 and 13 the blood and urine sugar curves do not exceed the normal limits, and the basal metabolism in these patients was 1 per cent below and 3 per cent above average normal, respectively. In general there is observed no parallelism between the lowering of the tolerance for glucose and the elevation of the basal metabolic rate in these patients. This observation is in keeping with the reported experience of others. Such a lack of parallelism is to be expected. The lowering of the tolerance for glucose depends upon many factors other than the functions of the thyroid gland. Moreover, the determination of the basal metabolic rate is a measure of the heat production under basal conditions, but the

conversion of glucose into glycogen, or of glycogen into glucose, involves an energy transformation of only 5 per cent of the total caloric value of the glucose. A study of the glucose tolerance and the basal metabolic rate affords more complete knowledge of the carbohydrate metabolism of the individual.

There appears to be no correspondence between the rate of basal metabolism and the Kottmann reaction. The maximum retardation of this reaction was obtained in Case 21, but there the basal metabolic rate was only 1 per cent above the average normal. In Case 16 only a ++ Kottmann reaction was noted, but the rate of basal metabolism was 86 per cent above the average normal. A normal Kottmann reaction was obtained in Case 10, but here the basal metabolic rate was 30 per cent above the average normal; but in Case 2 a ++ reaction was noted with a basal metabolism 1 per cent below average normal.

Determinations of urea nitrogen, uric acid and chlorids have been made on all of the control specimens of blood. Kottmann reactions were carried out on only those specimens of blood presenting normal figures for these three constituents. It will be seen that in the cases of hyperthyroidism there is noted in general a lower figure for the urea nitrogen of the control blood than in the other cases reported.

Twenty cases of epilepsy during the quiescent period have been studied. These results are recorded in Table II. These patients had not received medication previous to these tests. Of the 20 cases, 10 (Cases 1, 2, 4, 8, 9, 10, 11, 12, 15 and 19) show moderately lowered tolerance for glucose, whereas Case 5 had an increased tolerance. Considerable variation is noted in the basal metabolic rates. Four (Cases 8, 10, 11 and 19) have basal metabolic rates exceeding 10 per cent above the average normal, and in 2 (Cases 1 and 16) the basal metabolism is less than 10 per cent below average normal. Kottmann reactions, ranging from an accelerated to a strongly retarded reaction, have been obtained in these individuals. Here again no correspondence between the Kottmann reaction and the glucose tolerance or basal metabolism is noted. Furthermore, it was possible to demonstrate no relation between the Kottmann reaction and the frequency or the severity of the attacks.

Fifteen cases of psychoneurosis and 13, whose chief complaint was a severe headache of an undetermined etiology, are included in the series, and the data obtained on these subjects are reported in Tables III and IV. Normal blood and urine sugar curves after glucose were obtained in the majority of these cases. Some, however, exhibit a markedly lowered tolerance for carbohydrate. In Table III Cases 1, 2, 9, 10 and 11, and in Table IV Cases 11 and 13, belong to this group. Changes in the basal metabolism are within the normal range (10 per cent above or below the average normal) except in a few instances, and in these exceptions the

TABLE I.—THE KOTTMANN REACTION, GLUCOSE-TOLERANCE TEST AND BASAL METABOLISM IN THYROID DYSFUNCTION.

Case.	Age.	Sex.	Kottmann reaction.	Glucose tolerance test.			Blood findings.				Remarks.
				Test hour.	Blood sugar mg. per 100 cc.	Urine sugar mg. per hour.	Urea N. mg.	Uric acid mg.	Cl as NaCl mg.	Basal metabolic rate.	
1. D. W.	19	F.	+	Control	83	30					
				1st	214	1125	9.4	3.6	478	+4	Slight exophthalmos and enlarged thyroid; nervousness
				2d	170	1499					
2. M. R.	15	F.	++	Control	94	10					Goiter for 2 years; melancholia
				1st	149	48	9.5	2.1	445	−1	
				2d	117	59					
3. C. S.	26	F.	+	Control	85	11					Slight exophthalmos; tremor; nervousness
				1st	238	797	10.0	2.4	429	+32	
				2d	170	774					
4. C. G.	18	F.	+++	Control	107	18					Slightly enlarged thyroid; nervousness
				1st	214	369	10.6	2.7	478	+12	
				2d	142	623					
5. B. P.	16	M.	0	Control	90	67					Thyroid slightly enlarged
				1st	214	117	10.0	2.6	495	+15	
				2d	115	967					
6. F. L.	36	F.	++	Control	107	53					Thyroid slightly enlarged
				1st	250	285					
				2d	205	5382					
7. E. S.	29	F.	0	Control	105	70					Small goiter; weakness; nervousness
				1st	272	750	9.4	2.6	470	+13	
				2d	354	4210					
8. K. Y.	52	F.	0	Control	136	216					Moist skin; nervousness; pains, right side
				1st	306	328	11.3	3.3	495	+18	
				2d	220	180					
9. L. M.	31	F.	0	Control	91	82					Slight exophthalmos
				1st	165	...	7.8	2.5	495	+7	
				2d	300	221					
10 R. R.	43	F.	0	Control	124	38					Left thyroid adenoma, 5 years; nervousness
				1st	217	169	10.7	2.7	478	+30	
				2d	214	104					
11. B. H.	10	F.	0	Control	100	25					Thyroid very slightly enlarged; nervousness
				1st	125	...	10.4	4.5	478	−4	
				2d	158						
12. C. B.	31	M.	0	Control	83	46					Loss of weight; constipation; vertigo
				1st	195	94	8.7	3.5	470	+5	
				2d	155	104					
13. G. P.	12	F.	0	Control	94	13					Thyroid slightly enlarged
				1st	120	26	8.8	2.9	445	+3	
				2d	141	47					
14. S. W.	29	F.	++	Control	97	70					Swelling of neck, 3 years; headaches
				1st	150	45	10.2	5.0	479	+3	
				2d	143	28					
15. J. E.	18	M.	+	Control	91	81					Nervousness; thyroid very slightly enlarged
				1st	208	150	11.1	3.0	445	+13	
				2d	178	79					
16. G. P.		F.	++	Control	81	27					Loss of weight; very nervous
				1st	158	50	10.2	2.7	462	+86	
				2d	115	127					
17. E. B.	41	M.	++	Control	125	103					Loss of weight; nervousness; tremor
				1st	220	158	11.1	3.4	462	+28	
				2d	148	248					
18. S. T.	47	F.	+++	Control	88	39					Loss of weight; swelling of neck; nervousness
				1st	200	531	11.1	3.4	478	+34	
				2d	155	112					
19. R. L.	28	F.	+++	Control	71	26					Nervousness; headaches
				1st	167	54	10.5	2.5	470	+9	
				2d	144	610					
20. M. S.	14	F.	++	Control	83	31					General tremor; nervousness; moist skin
				1st	112	20	9.5	2.1	519	+25	
				2d	158	36					
21. M. S.	14	F.	++	Control	125	53					Thyroid palpable; mental insufficiency
				1st	230	476	11.5	2.8	478	+1	
				2d	143	950					

0 = Normal
− = Accelerated
+ = Slightly retarded
++ = Retarded
+++ = Markedly retarded
++++ = Strongly retarded

TABLE II.—THE KOTTMANN REACTION, GLUCOSE-TOLERANCE TEST AND BASAL METABOLISM IN EPILEPSY.

Case.	Age.	Sex.	Kottmann reaction.	Glucose tolerance test.			Blood findings.				Remarks.
				Test hour.	Blood sugar mg. per 100 cc.	Urine sugar mg. per hour.	Urea N. mg.	Uric acid mg.	Cl as NaCl mg.	Basal metabolic rate.	
1. I. S.	13	F.	++++	Control	83	77					
				1st	155	47	10.6	2.5	495	−9	Epilepsy for 7 years
				2d	146	64					
2. S. P.	12	M.	0	Control	106	76					
				1st	134	63	12.1	3.6	478	−13	Epileptic attack for 2 mos.
				2d	144	73					
3. S. R.	12	M.	+++	Control	82	13					
				1st	105	41	17.0	3.2	495	−3	Epilepsy for 6 years
				2d	104	27					
4. S. E.	19	F.	++++	Control	97	46					
				1st	143	24	11.2	2.5	495	−1	Epilepsy for 10 years; thyroid slightly enlarged
				2d	123	54					
5. R. A.	12	M.	+	Control	88	25					
				1st	91	28	14.0	2.8	445	−5	Epilepsy; poor memory
				2d	91	26					
6. A. K.	18	M.	0	Control	83	18					
				1st	113	16	13.7	4.1	462	+4	Jacksonian; epilepsy for 4 years
				2d	91	20					
7. C. R.	14	M.	+++	Control	107	18					
				1st	122	16	10.9	1.9	478	+8	Epilepsy for several years
				2d	110	20					
8. S. K.	22	M.	++	Control	90	10					
				1st	140	18	10.9	3.0	429	+22	Epilepsy; mitral systolic murmur
				2d	144	790					
9. C. C.	29	F.	0	Control	100	20					
				1st	157	158	11.1	2.8	445	+5	Epilepsy for 11 years
				2d	130	...					
10. W. L.	19	M.	+++	Control	81	45					
				1st	187	62	12.0	3.4	445	+11	Epilepsy for few years
				2d	125	214					
11. L. P.	25	M.	−	Control	73	20					
				1st	139	15	9.5	3.0	445	+11	Epilepsy
				2d	127	17					
12. D. F.	27	F.	0	Control	83	11					
				1st	147	...	12.1	2.7	495	+1	Epilepsy?
				2d	122	37					
13. I. F.	15	F.	+	Control	84	27					
				1st	93	25	13.0	...	495	+3	Epilepsy for 2 years
				2d	115	32					
14. H. R.	14	F.	0	Control	105	10					
				1st	157	16	8.3	2.5	495	−5	Epilepsy for 2 years
				2d	130	5					
15. A. M.	31	F.	+++	Control	68	25					
				1st	136	36	10.6	2.4	503	−4	Epilepsy for 6 years
				2d	163	18					
16. D. F.	21	F.	0	Control	81	60					
				1st	125	27	8.5	3.0	495	−14	Epilepsy
				2d	96	41					
17. H. S.	24	M.	0	Control	88	28					
				1st	104	10	10.6	3.2	486	−5	Epilepsy
				2d	124	10					
18. L. W.	27	M.	+++	Control	85	60					
				1st	121	21	11.9	2.5	478	+1	Epilepsy
				2d	113	15					
19. E. H.	16	M.	+++	Control	108	47					
				1st	183	24	9.6	3.1	478	+18	Epilepsy
				2d	124	13					
20. W. L.	37	M.	0	Control	78	44					
				1st	115	20				−9	Epilepsy
				2d	95	29					

TABLE III.—THE KOTTMANN REACTION, GLUCOSE-TOLERANCE TEST AND BASAL METABOLISM IN PSYCHONEUROSES.

Case.	Age.	Sex.	Kottmann reaction.	Glucose tolerance test.			Blood findings.				Remarks.
				Test hour.	Blood sugar mg. per 100 cc.	Urine sugar mg. per hour	Urea N. mg.	Uric acid mg.	Cl as NaCl mg.	Basal metabolic rate.	
1. W. T.	35	M.	+	Control	85	44					Melancholia; depression
				1st	231	240	10.8	4.1	462	−11	
				2d	250	2600					
2. E. D.	45	M.	0	Control	75	87					Very nervous
				1st	205	68	11.4	3.9		−8	
				2d	238	225			...		
3. J. S.	44	F.	+	Control	80	54					Nervousness; loss of weight
				1st	138	90	10.4	3.1	493	−15	
				2d	100	47					
4. I. H.	23	M.	+++	Control	82						Nervousness for 6 years
				1st	155	...	12.4	2.6	478	−8	
				2d	125						
5. W. L.	67	M.	0	Control	76	31					Emotional instability
				1st	160	169	12.5	3.3	495	+18	
				2d	172	19					
6. M. R.	29	M.	++	Control	79	35					Nervousness
				1st	183	160	9.3	3.5	478		
				2d	108	433					
7. L. S.	54	F.	+	Control	90	60					Nervousness
				1st	242	41	16.1	4.2	460	+6	
				2d	161	412					
8. H. J.	20	F.	0	Control	81	177					Nervousness
				1st	146	599	9.6	3.9	478	−4	
				2d	111	489					
9. F. H.		M.	0	Control	87	28					Nervousness irritable
				1st	282	418	9.7	3.1	462	−3	
				2d	246	1366					
10. A. H.	30	F.	0	Control	77	55					Nervousness; melancholia for 2 years
				1st	203	684	10.3	2.9	445	−2	
				2d	178	966					
11. L. H.	25	F.	0	Control	88	22					Very nervous
				1st	211	30	14.4	2.9	478	−6	
				2d	135	211					
12. S. A.	10	M.	+++	Control	107	20					Nervousness; mental defective
				1st	132	...	12.4	2.0	495	−11	
				2d	130	70					
13. D. S.	32	F.	++++	Control	76	37					Nervousness; mental depression
				1st	153	23	9.3	2.4	495	+3	
				2d	123	30					
14. F. N.	38	F.	++++	Control	86	17					Nervousness
				1st	149	63	12.3	2.7	495		
				2d	111	70					
15. B. G.	35	F.	+++	Control	102						Nervousness; had child 4 months ago
							11.4	3.1	478	+12	

variations from the normal range are not great. The results with the Kottmann test varied from normal to strongly retarded reactions.

In Table V are reported the findings on normal and miscellaneous mental cases. The patients considered in this group gave no clinical evidence of thyroid dysfunction. In the majority of these individuals normal blood and urine sugar curves have been obtained after the glucose ingestion. However, Cases 1, 4 and 6 show a subnormal tolerance for carbohydrate. There is noted also considerable variation in the basal metabolic rates, 3 having basal metabolism less than −10 per cent and 4 more than +10 per cent. In this group normal Kottmann reactions were obtained in 8 cases, slightly accelerated in 4 and retarded in 4. Case 11 alone gave a

TABLE IV.—THE KOTTMANN REACTION, GLUCOSE-TOLERANCE TEST AND BASAL METABOLISM IN CASES COMPLAINING OF HEADACHE.

Case.	Age.	Sex.	Kottmann reaction.	Glucose tolerance test.			Blood findings.				Remarks.
				Test hour.	Blood sugar mg. per 100 cc.	Urine sugar mg. per hour.	Urea N. mg.	Uric acid mg.	Cl as NaCl mg.	Basal metabolic rate.	
1. V. C.	15	M.	++	Control	82	22					Headaches, lethargic encephalitis
				1st	167	28	8.7	4.2	462	+15	
				2d	117	...					
2. L. H.	44	M.	0	Control	93	45					Headaches
				1st	124	24	14.1	3.0	478	−3	
				2d	78	26					
3. R. D.	28	F.	+	Control	88	75					Headaches; depression for 2 years
				1st	200	567	11.3	2.7	495	−1	
				2d	114	586					
4. U. W.	51	M.	+++	Control	99	78					Headaches; loss of weight
				1st	217	100	13.1	3.8	503	−5	
				2d	115	136					
5. R. L.	28	F.	+++	Control	71	26					Headaches; nervousness
				1st	167	54	10.5	2.5	470	+9	
				2d	144	610					
6. A. G.	24	M.	++	Control	75	19					Headaches; depression
				1st	185	43	12.8	3.8	...	±0	
				2d	83	43					
7. I. M.	18	M.	+++	Control	73	24					Headaches; nervousness
				1st	114	20	10.0	3.7	...	−2	
				2d	103	25					
8. E. L.	52	M.	++	Control	104	63					Headaches
				1st	139	40	14.7	3.8	...	−12	
				2d	172	54					
9. L. S.	44	F.	+++	Control	81	19					Headaches
				1st	141	15	11.5	2.3	495	+10	
				2d	98	24					
10. W. H.	11	M.	++	Control	88	10					Headaches
				1st	156	22	12.8	2.8	462	−5	
				2d	110	32					
11. J. L.	55	M.	++++	Control	93	24					Headaches; high blood pressure
				1st	312	145	12.2	2.7	462	−3	
				2d	333	3000					
12. B. S.	32	F.	++++	Control	87	30					Headaches; had bromid 10 days ago
				1st	103	34	9.4	2.2	495	−1	
				2d	110	273					
13. B. G.	30	F.	−	Control	89	30					Headaches; irritable
				1st	208	36	11.1	2.3	462	+9	
				2d	197	10					

strongly retarded reaction. Here again no correspondence is seen between the results of glucose-tolerance test, basal metabolism or Kottmann reactions.

A comparison of the Kottmann reaction on bloods obtained during the fasting state and one hour after the ingestion of glucose has been made in Table VI to determine the influence of an increase in blood sugar upon the reaction. Subject I had a high tolerance for carbohydrate, so that the intake of the glucose did not bring the blood sugar beyond the normal limit. In the remaining cases, however, hyperglycemias were noted one hour after the glucose ingestion. The fasting blood of Case 1 gave a slightly retarded reaction, but the fasting bloods of the other cases presented normal reactions. The reactions on the bloods drawn following the glucose intake did not significantly vary from the reactions obtained in the fasting bloods. In Cases 3 and 5 a slight acceleration of the reaction is produced, but in Case 4 a slight retardation results, but these changes are not sufficient to render the reactions abnormal.

TABLE V.—THE KOTTMANN REACTION, GLUCOSE-TOLERANCE TEST AND BASAL METABOLISM IN MISCELLANEOUS CASES.

Case.	Age.	Sex.	Kottmann reaction.	Glucose tolerance test.			Blood findings.				Remarks.
				Test hour.	Blood sugar mg. per 100 cc.	Urine sugar mg. per hour.	Urea N. mg.	Uric acid mg.	Cl as NaCl mg.	Basal metabolic rate.	
1. G. P.	16	F.	0	Control	130	21					Depression
				1st	180	240	9.9	...	...	−5	
				2d	147	153					
1. F. J.	36	M.	0	Control	87	107					Depression; backache
				1st	126	111	9.7	4.1	460	+0	
				2d	123	65					
3. A. F.	14	M.	0	Control	93	54					Idiot; mentally backward
				1st	192	21	12.0	2.6	470	−4	
				2d	115	63					
4. H. F.	11	M.	−	Control	86	57					Intellectual instability; emotionally unstable
				1st	167	18	10.9	2.7	478	−23	
				2d	174	633					
5. L. H.	12	M.	0	Control	100	48					Physically normal
				1st	178	46	12.0	3.4	493		
				2d	119	39					
6. M. H.	11	M.	0	Control	100	36					Obesity; mental defective
				1st	313	634	10.7	3.4	462	+14	
				2d	214	732					
7. B. M.	7	M.	+	Control	82	36					Physically normal
				1st	111	13	11.2	2.4	503	−12	
				2d	92	34					
8. C. A.	24	M.	0	Control	83	34					Depression both mentally and physically
				1st	100	32	9.4	2.7	495	+2	
				2d	92	44					
9. S. W.	7	M.	+	Control	83	20					Mentally backward
				1st	99	15	9.2	2.1	495	−19	
				2d	106						
10. R. P.	11	F.	−	Control	94	15					Physically normal
				1st	110	57	12.0	2.2	495	−4	
				2d	93	10					
11. J. R.	15	M.	+++	Control	88	10					Mentally and physically backward
				1st	101	20	11.0	...	...	+1	
				2d	79	18					
12. W. J.	36	M.	0	Control	86	24					Physically normal
				1st	150	59	9.9	3.4	478	+25	
				2d	100	45					
13. P. K.	14	M.	0	Control	82	116					Physically normal
				1st	167	32	9.5	3.6	462	+15	
				2d	119						
14. W. L.	37	M.	0	Control	78	44					Obesity; pain in back
				1st	115	20	17.7	3.2	486	+19	
				2d	95	29					
15. M. E.	14	F.	−	Control	79	15					Physically norma
				1st	111	12	9.5	2.0	429	−2	
				2d	130	13					
16. H. R.	30	F.	+	Control	79	16					Physically normal
				1st	93	25	12.1	2.5	445	−6	
				2d	107	25					
17. H. P.	13	M.	++	Control	79	24					Emotional instability; precocity
				1st	101	5	10.7	2.4	478	−5	
				2d	100	25					
18. J. M.	17	M.	−	Control	90	27					Mentally backward
				1st	104	32	9.3	3.0	429	+19	
				2d	110	42					
19. V. M.	14	F.	0	Control	71	43					Mentally defective
				1st	142	175	12.0	2.6	470	+9	
				2d	141	103					
20. K. M.	26	M.	0	Control	90	33					Emotional instability
				1st	189	24	11.1	2.3	462	−17	
				2d	103	22					
21. V. P.	9	M.	+	Control	93	27					Mentally defective
				1st	182	22	11.7	3.0	495	+13	
				2d	135						

TABLE V.—THE KOTTMANN REACTION, GLUCOSE-TOLERANCE TEST AND BASAL METABOLISM IN MISCELLANEOUS CASES.—(*Continued.*)

Case.	Age.	Sex.	Kottmann reaction.	Glucose tolerance test.			Blood findings.				Remarks.
				Test hour.	Blood sugar mg. per 100 cc.	Urine sugar mg. per hour.	Urea N. mg.	Uric acid mg.	Cl as NaCl mg.	Basal metabolic rate.	
22. D. B.	22	F.	0	Control	81	32					Emotional instability
				1st	107	50	11.3	2.8	470	+4	
				2d	91	16					
23. O. R.	21	M.	0	Control	80	76					Mentality of 9 years
				1st	167	799	11.3	3.1	478	+18	
				2d	97	144					
24. W. M.	8	M.	0	Control	88	25					Physically normal
				1st	114	10	12.4	2.5	478	−5	
				2d	75	10					
25. K. G.	22	F.	−	Control	88	58					Lethargic encephalitis
				1st	142	67	12.4	3.1	478	+8	
				2d	122	55					
26. J. F.	8	M.	0	Control	79	10					Physically normal
				1st	111	21	13.4	3.2	478	−3	
				2d	115	10					
27. C. G.	3	M.	−	Control	96	9					Emotional instability
				1st	100	11	10.0	2.6	495		
				2d	135	...					
28. A. M.	6	M.	0	Control	84	22					Emotional instability
				1st	106	26	10.4	2.0	495		
				2d	106	20					
29. M. P.	53	M.	−	Control	86	32					Tonsillitis
				1st	187	66	14.3	2.7	495	−6	
				2d	164	52					
30. D. S.	48	M.	0	Control	82	12					Nervousness; lassitude
				1st	172	14	16.1	2.5	478	−15	
				2d	101	109					
31. D. K.	10	F.	0	Control	88	18					Mentally defective
				1st	130	50	9.1	3.2	478	−5	
				2d	150	43					
32. E. M.	11	M.	+	Control	91	12					Emotional instability
				1st	114	10	12.6	2.4	495	+6	
				2d	90	10					

The observations on the 101 cases discussed in the course of the paper have been summarized in Table VII. Of the 21 cases of clinical hyperthyroidism none gave accelerated reactions, 38 per cent normal, 14 per cent slightly retarded and 48 per cent retarded. Of the 20 cases of epilepsy, 5 gave normal reactions, but otherwise their response to this test is very similar to the hyperthyroids. Subjects with neuropsychosis gave reactions analogous to the hyperthyroids; however, a slightly higher fraction presented slightly retarded, and a slightly smaller fraction retarded, reactions. The maximum percentage of retarded reactions were obtained in patients whose chief complaint was headache of no definite etiology. Of these, 76 per cent presented retarded, 8 per cent slightly retarded, 8 per cent normal, and 8 per cent accelerated, reactions. Among the miscellaneous cases, with no clinical or laboratory evidence of hyperthyroidism, normal reactions were seen in 53 per cent, accelerated in 25, slightly retarded in 15 and retarded in 6 per cent.

That there is no relation between the tolerance for glucose and the Kottmann reaction is evident from Table VIII. Of the patients exhibiting a lowered tolerance for glucose, 35 per cent gave normal

TABLE VI.—COMPARISON OF KOTTMANN REACTION BETWEEN FASTING AND ONE HOUR AFTER GLUCOSE INGESTION.

Case.		Blood sugar mg. per 100 cc.	2½ min.	5 min.	10 min.	15 min.	20 min.	30 min.
1. I. Z.	Control	84	0	0	L	L	D	D
	One hour after glucose	93	0	0	L	L	D	D
2. S. E.	Control	105	0	L	L	D	D	D
	One hour after glucose	272	0	F	L	D	D	D
3. V. A.	Control	71	0	F	L	D	D	D
	One hour after glucose	142	0	L	L	D	D	D
4. K. M.	Control	90	0	L	L	D	D	D
	One hour after glucose	182	0	F	L	D	D	D
5. K. Y.	Control	136	0	F	L	D	D	D
	One hour after glucose	306	0	L	L	D	D	D

1.75 gm. of glucose per kilogram of body weight in 50 per cent solution by mouth.
0 = No color change
F = Faint yellow brown
L = Light brown
D = Dark brown

TABLE VII.—THE KOTTMANN REACTION IN 101 CASES OF DIFFERENT DISEASES.

	No. of cases.	Kottmann reaction.							
		Accelerated.		Normal.		Slightly retarded.		Retarded.	
		Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.
Hyperthyroidism	21	0	0	8	38	3	14	10	48
Epilepsy	20	1	5	8	40	2	10	9	45
Neuropsychosis	15	0	0	6	40	3	20	6	40
Cases complaining of headache	13	1	8	1	8	1	8	10	76
Miscellaneous	32	8	25	17	53	5	15	2	6
Total	101	10		40		14		37	

Kottmann reactions and 38 per cent retarded, but of the subjects with normal tolerance, only 42 per cent presented normal reduction of the silver iodid and 35 retarded. A similar comparison between the basal metabolic rate and the Kottmann reaction has been made in Table IX. Of those subjects with basal metabolism exceeding 10 per cent above average normal, 37 per cent gave normal and 40 per cent retarded reactions. In the second group, comprising cases whose basal metabolic rate ranged within the limits of 10 per cent above to 10 per cent below average normal,

TABLE VIII.—THE KOTTMANN REACTION COMPARED WITH GLUCOSE-TOLERANCE FINDINGS.

	Cases.	Kottmann reaction.					
		Accelerated.	Normal.		Slightly retarded.	Retarded.	
			Number.	Per cent.		Number.	Per cent.
Lowered glucose tolerance	39	4	14	35	6	15	38
Normal glucose tolerance	59	6	25	42	7	21	35
High glucose tolerance	3	..	1	..	1	1	..
Total	101	10	40		14	37	

TABLE IX.—THE KOTTMANN REACTION COMPARED WITH BASAL METABOLISM.

Basal metabolism rate.	Cases.	Kottmann reaction.					
		Accelerated.	Normal.		Slightly retarded.	Retarded.	
			Number.	Per cent.		Number.	Per cent.
Above +10	27	2	10	37	4	11	40
+10 to −10	57	5	24	42	6	22	38
Below −10	12	2	4	33	4	2	16
Total	96	9	38		14	35	

normal reactions were obtained in 42 per cent of the cases, and retarded reactions in 38 per cent. But a smaller fraction of retarded reaction (16 per cent) were noted in patients with basal metabolic rates less than 10 per cent below average normal.

Conclusions. It is generally conceded among physiologists and clinicians that the determination of the basal metabolic rate is the most dependable laboratory index of thyroid activity. Increased thyroid secretion produces a lowering of the tolerance for carbohydrate, but there are numerous other conditions in which the tolerance for carbohydrate may be diminished. Hence the occurrence of high blood and urine sugar curve after the ingestion of glucose is not in itself indicative of hyperthyroidism. However, in hyperthyroidism the blood and urine sugar curves after glucose furnish information concerning a phase of carbohydrate metabolism which is not gauged by the basal metabolic rate.

The basis of the Kottmann reaction is obscure, and hence it is difficult to say in what manner thyroid activity influences it.

Such a reaction can only be accepted with skepticism. From the data reported in this paper it is evident that the results of the Kottmann reaction are not in accord with the basal metabolism or the glucose tolerance. The retardation of the reduction of the silver iodide to silver occurs in many and various conditions patently not due to hyperthyroidism. Its diagnostic value in detecting hyperfunction or hypofunction of the thyroid is very dubious. It cannot be accepted as a substitute for the determination of the basal metabolic rate or of the glucose tolerance.

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THE LACK OF UNIFORMITY IN THE INSULIN REACTION.

By Henry J. John, M.D.,

CLEVELAND, OHIO.

(From the Cleveland Clinic.)

Shortly after the discovery of insulin, Banting and his coworkers described the reactions to insulin in rabbits. They attributed these reactions to the hypoglycemia which develops several hours after the injection, and found that they could be overcome by the injection of glucose. Collip,[1] who has made similar experiments, also stressed this point.

Before presenting an analysis of my own series in which a reaction occurred, it may be well to describe the symptoms which are indicated by this term. The outstanding symptoms in the usual order of their occurrence are the following: (1) A feeling of anxiety; (2) pallor of the skin; (3) increased pulse rate and slight tremor of the hands; (4) a "sinking spell," the patient feeling very weak and exhausted; (5) voracious hunger; (6) perspiration all over the body so profuse that the clothing may be drenched. Children will suddenly cry out (even from a sound sleep) as though terrified and in children also a marked convergent nystagmus is often seen during a severe reaction. Any or all of these symptoms may appear. Often, especially in the early days of insulin, I used no antidote, as it seemed important to watch the development and the progress of these symptoms in order to see whether or not the human organism could right itself without aid. It can and will, though the reaction is usually followed by a more prolonged period of exhaustion than when an antidote is employed, and I have seen no bad effects. However,

a reaction can be cut short by the use of orange juice, by sugar dissolved in hot water, or still more quickly by a teaspoonful of whiskey and a teaspoonful of sugar in a cup of hot water.

In my work with diabetic patients, however, it soon became evident that there is no definite relationship between the degree of hypoglycemia and the reaction, for large doses of insulin sometimes produce no reaction even when the blood-sugar content has reached the value of 45 mg. per 100 cc. or less or, if it does occur, the reaction may come a long time after the hypoglycemia is established. Moreover, the injection of calcium will eliminate the reaction without increasing the blood-sugar value. An analysis of all cases in my series in which a reaction occurred, including observations of the blood-sugar content before and at the time of the reaction and of the time interval between the administration of insulin and the occurrence of the reaction, showed that in 54 per cent of the cases the reaction apparently coincided with hypoglycemia, while in 46 per cent the reaction occurred when normal glycemia or even hyperglycemia was present. Moreover, as is shown by the accompanying charts, even in the same patient the reaction to insulin varies. Thus, a patient may have a low blood-sugar content on one day, yet show no reaction even to large or repeated doses of insulin, and on another day when his blood sugar is at a much higher level, a smaller dose of insulin may produce a marked reaction. Thus, for example, a patient with such a marked hypoglycemia as 60 or even 48 to 50 mg. per 100 cc. of blood may show no reaction after the intravenous injection of from 20 to 40 units of insulin. It is obvious, therefore, that many of these reactions must be due to something else than hypoglycemia. Eadie, Macleod and Noble[2] have shown that after the administration of insulin muscular irritability is increased. Behrendt and Hopmann[3] confirmed this finding and added the observation that the status of increased muscular irritability is initiated after the lowest hypoglycemic level has been reached. According to Macleod, the insulin injection gives rise to certain toxic metabolic products which irritate the centers in the posterior part of the brain and thus elicit the muscle cramps. On the other hand, Olmstead and Logan[4] found that cramps followed the injection of insulin in decerebrated cats, but not in decapitated cats, or even after section of the spinal cord. They think that in hypoglycemia a state of anoxemia arises, which is manifested in the dark color of the blood, with resultant irritation of the bulbar centers. They find many analogies between hypoglycemia and asphyxia.

Hepburn and Latchford[5] showed that a rabbit's heart which has been perfused by Locke's solution does not lose any of its glycogen when insulin is added; and Schwartz and Bricka[6] found that the amount of glycogen in the liver is not changed even after the injection of large doses of insulin.

Karasek[7] measured the muscular irritability of frogs after the injection of insulin by means of the faradic current and came to the conclusion that insulin does not alter the irritability of muscle; and that the character of the muscle spasms which follow the injection of insulin shows that they are not due to irritation of the motor centers as, if they were, they would occur spontaneously. He concludes that they should be considered as merely the expression of an increased reflex irritability.

Case Reports. The following case reports with the accompanying charts will serve to illustrate the marked variations on successive days in the response of the same patients to the injection of insulin.

CASE I.—This patient was a married woman, aged forty-nine years. There was no familial history of diabetes. Of the childhood diseases she had had measles, mumps, chickenpox, and whooping cough, and later in life she had had grippe, tonsillitis and malaria. One and a half years before she had suffered from thirst, polyuria and nocturia and had lost 55 pounds (63 per cent) in weight. Sugar was found in the urine and a restricted diet was prescribed. Her condition improved, but she grew careless in her diet and the symptoms reappeared. When she consulted me she was having cramps in her legs and her vision was blurred. Her ankles were swollen, she was short of breath on exertion and had pain in the region of her heart. She kept increasing her diet because she was losing weight and continually getting weaker.

When she presented herself for examination she was very emaciated. Her blood sugar was 490 mg. per 100 cc.; plasma acetone 3 plus; there was heavy glycosuria; the blood urea was 75 mg.; blood creatinin 1.4 mg.; the Wassermann test was negative.

The patient's daily progress is illustrated in Chart I in which one can follow the daily blood-sugar fluctuation, as indicated by the several blood-sugar estimations made each day. (N.B.—When three blood-sugar estimations are made daily it is to be understood that one is made immediately before each meal; when more than three estimations are made in a day, they are made at intervals between 8 A.M. and 5 P.M.)

Chart II shows the fluctuations in the blood-sugar content of this patient on nine successive days, during which time she received varying doses of insulin as indicated on the chart. Throughout this period the patient received a uniform daily diet.

A study of this chart shows that the blood sugar dropped but little, or sometimes even rose during the morning, while there was a fairly uniform drop during the afternoon. Nevertheless the response to equal doses of insulin was far from uniform. On the first day, when frequent doses of insulin were given, the drop in the blood-sugar curve was most pronounced, perhaps because the blood sugar was the highest on that day and the patient was unac-

customed to insulin. On March 20th there was a rise after the first dose of insulin followed by a continued drop for the next four hours with a subsequent rise of the blood sugar. On this day the first dose was followed by breakfast which might explain the rise of blood sugar, provided a sufficient dose of insulin was not given to offset

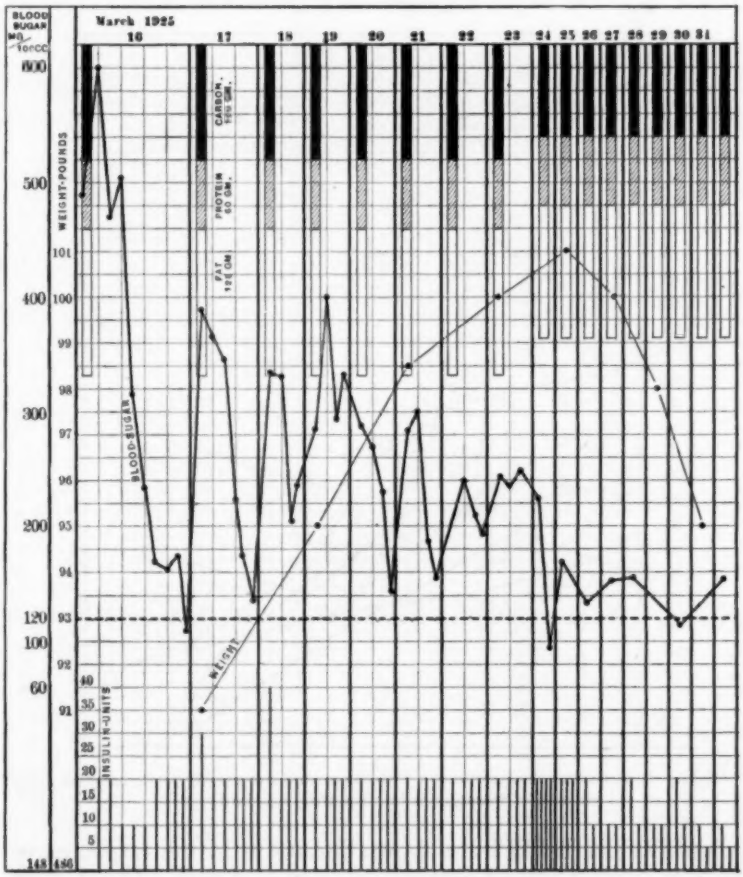

CHART I.—The daily progress of Case I. Columns above represent the diet, the black portion representing the carbohydrate content (each square equals 20 gm.), the shaded portion the protein content, the light portion the fat content. The heavy curve shows the blood-sugar variations. The light curve shows the variations in body weight. Insulin dosage is indicated at the bottom of the chart in heavy upright lines.

the postprandial effect. However, between the second and third doses on this day the noon meal was taken and yet there was a continued fall in the blood sugar. It is possible of course that this difference between the afternoon and the morning effects of insulin may have been due to a cumulative effect, but it would hardly seem as if that could be the case since all doses were given intravenously.

On March 24th, there was no drop in the blood sugar whatever, and in spite of the repeated doses of insulin there was only a very slight drop on the preceding day.

On the whole, then, while in this case there was a general average similarity in the responses to the injection of insulin, there were marked variations in the responses on successive days.

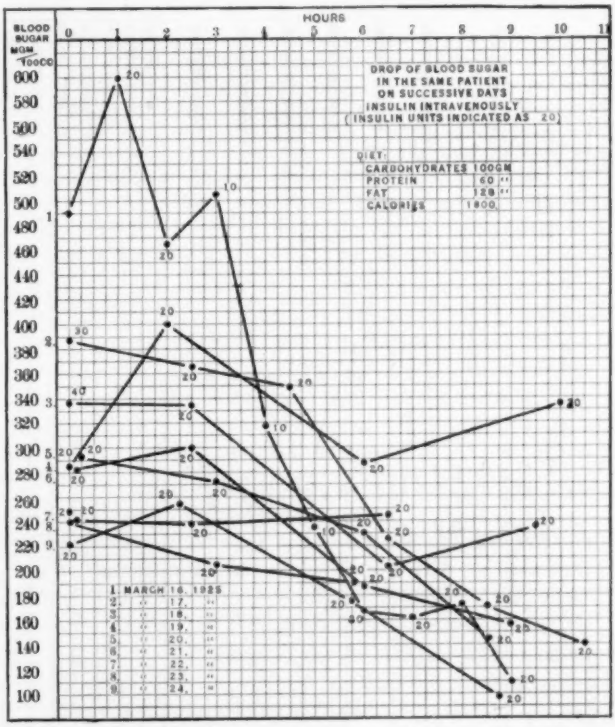
HOURS
BLOOD SUGAR MGM. PER 100CC
DROP OF BLOOD SUGAR IN THE SAME PATIENT ON SUCCESSIVE DAYS INSULIN INTRAVENOUSLY (INSULIN UNITS INDICATED AS 20)
DIET:
CARBOHYDRATES 100GM
PROTEIN 60 "
FAT 120 "
CALORIES 1900
1. MARCH 16, 1925
2. " 17. "
3. " 18. "
4. " 19. "
5. " 20. "
6. " 21. "
7. " 22. "
8. " 23. "
9. " 24. "

CHART II.—Blood-sugar fluctuations in Case I on nine successive days; varying doses of insulin were given but the diet was uniform.

CASE II.—In Table I are shown variations in the responses to insulin in another patient over a longer period of time. This patient was a little girl, aged six years who, at the age of four years, developed diabetes after an attack of measles.* In this case there were marked variations in the blood-sugar content in response both to somewhat moderate and to very large doses of insulin. For each of these estimations the blood was taken immediately before each meal and the insulin was administered intravenously at the same time. Although very large doses of insulin were given during January (100 units intravenously twice daily) to such a young child, yet no insulin reaction occurred at any time during that period.

* For a complete chart showing the progress of this patient see Med. J. and Rec., 1924, **119**, 229.

TABLE I.—VARIATIONS IN THE RESPONSE TO INSULIN IN THE SAME PATIENT.

	Insulin dosage.			Blood sugar (mg. per 100 cc.).		
	8.30 A.M.	11.30 A.M.	4.30 P.M.	8.30 A.M.	11.30 A.M.	4.30 P.M.
1923.						
Oct. 22	32	20	20	288	220	320
23	32	20	20	326	288	239
24	30	20	20	313	129	246
25	35	20	20	255		309
26	32	22	22	285	256	285
27	34	20	20	272	218	190
28	32		34	226		476
29	36	30	30	265	447	200
30	42	32	32	277	228	213
31	36	30	30	272	248	180
Nov. 1	34	40	31	228	342	238
2	36		30	237		301
3	42		42	223		340
8	50	50		149	305	
9	52	52	50	255	166	
10	50	50	50	241	208	140
12	50	50	50	282	138	
13	50	50	50	260	275	
14	50	50	52	251	181	193
15	50	50	50	210	154	167
16	50	50	50	230	138	171
17	50	50	50	300	127	88
18	50	50	50	256	110	
19	50	50	50	194	57	188
20	50	50	50	144	288	136
21	50	50	50	170		146
22	50	50	50	166	98	117
23	50	50	50	195	100	104
24	50	50	50	251	90	
25	50		50	323		196
26	50	50	50	208	133	132
27	50	50	50	220		105
28	50	50	50	222	67	137
Dec. 24	50		35	212		158
28	70		70	236		248
29	70		72	256		234
30	84		80	293		270
31	80		70	167		357
1924.						
Jan. 2	100		100	226		300
3	100		100	334		244
4	100		100	322		278
5	100		100	325		312
7	100		100	252		235
8	100		100	186		234
9	100		100	277		203
10	100		100	222		316
11	100		100	224		292
12	100		100	277		168
13	100		100	342		305
14	100		100	255		282
15	100		100	312		296
16	100		100	250		230
17	100		100	244		288
18	100		100	228		267
19	100		100	177		220
21	100		100	195		186

TABLE I.—VARIATIONS IN THE RESPONSE TO INSULIN IN THE SAME PATIENT.—*Continued*

	Insulin dosage.			Blood sugar (mg. per 100 cc.).		
	8.30 A.M.	11.30 A.M.	4.30 P.M.	8.30 A.M.	11.30 A.M.	4.30 P.M.
22	100		100	280		267
23	100		100	288		210
24	100		100	308		274
25	100		100	233		210
Feb. 5	20	20	20	220	190	255
6	20	20	20		192	267
7	20	20	20	300	253	227
8	20	20	20	240		264
11	20		30	210		310
13	20		28	282		194
14	24		24	274		197
15	26		30	262		317
16	26		26	262		335
18	24		23	280		310
19	30		30	245		290
20	30		30	184		252
21	30		26	204		275
22	28		20	178		247
25	20		20	283		384
26	22		20	244		278
Oct. 22	20	20	20	250	272	275
23	20	20	20	242	228	388
24	20	20	20	402	331	314
25	20	20	20	328	252	

From October 22 to November 3 the diet consisted of 2000 calories, carbohydrates 100, proteins 70, fats 146; from November 8 to February 26 it consisted of 1700 calories, carbohydrates 80, proteins 60, fats 126; from October 22 to October 25, 1600 calories, carbohydrates 70, proteins 50, fats 133.

Some months later, however, when the insulin dosage had been reduced to 20 units three times a day, one reaction did develop suddenly. During the whole period of two and a half years this child has had only three reactions.

I do not wish it to be understood that I am advocating the use of huge doses of insulin. My purpose is only to demonstrate from this history the extreme tolerance for insulin in a very young patient, and to show how safely very large doses may be given. The problem which I was trying to solve when I gave these very large doses was the following: Will large doses of insulin accomplish more than frequent smaller doses, that is, will they enable the patient to maintain a lower blood-sugar level? The answer to this question as indicated by the trial of large doses for almost a month is, that although large doses may safely be administered, they are of no more avail than are small doses.

Chart III shows graphically the reactions which followed the administration of insulin in a group of 17 patients. This chart shows insulin reactions in their relation (*a*) to the length of time between the administration of insulin and the reaction; (*b*) to the dosage of insulin; and (*c*) to the blood-sugar value before the insulin was given and at the time of the reaction.

In some cases, as shown by the chart, the reaction occurred promptly; in others it did not occur until several hours after the insulin was given. It will be noted also that apparently the occurrence of the reaction bears no relation either to the height of the blood sugar or to the number of units of insulin administered. Moreover, there is apparently no uniform relation between the dosage of insulin and the degree of the subsequent fall of the blood sugar.

Tables II to VI show the variations in the reactions to insulin in 24 patients classified according (1) to the blood-sugar content

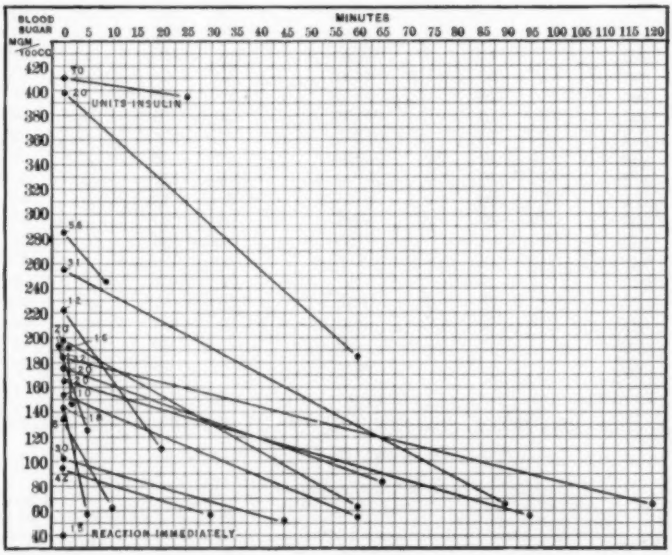

CHART III.—Insulin reactions in 17 cases. The dosage of insulin is that indicated by the figures enclosed in circles. The length of each line indicates the period between the administration of the insulin and the occurrence of the reaction.

before the insulin was given; (2) to the insulin dosage; (3) to the blood-sugar content when the reaction occurred; (4) to the length of time between the administration of insulin and the reaction; and (5) to the age of the patient. If we consider that 80 mg. glucose per 100 cc. or less indicates a hypoglycemia, then the information given in these tables may be summarized as follows:

		Per cent.
Total number of cases	24	
Cases in which reaction occurred during hypoglycemia	13	54.16
Cases in which reaction occurred in the presence of normal glycemia or hyperglycemia	11	45.84

This shows then that the general statement which is prevalent in the literature that an insulin reaction indicates a marked state of hypoglycemia is far from true.

TABLE II.—REACTIONS TO INSULIN OF 24 PATIENTS IN RELATION TO BLOOD-SUGAR VALUE IMMEDIATELY BEFORE INSULIN WAS GIVEN.

Blood sugar before administration of insulin (mg. per 100 cc.).	Insulin dosage (units).	Time between administration of insulin and reaction (minutes).	Blood sugar at time of reaction (mg. per 100 cc.).	Age of patient (years).
410	30	25	394	12
405	10	75	66	11
400	20	60	186	51
384	20	15	340	12
288	20	10	202	14
287	20	9	285	14
286	56	8	246	34
236	31	90	67	57
222	12	20	110	32
197	20	60	62	55
196	20	5	125	50
194	10	55	52	59
191	16	2	147	9
184	32	120	65	66
179	20	30	122	47
175	20	65	83	55
167	20	95	57	36
153	10	60	55	50
141	18	5	58	46
133	5	10	61	9
104	20	60	41	45
102	30	45	51	32
93	42	30	59	22
40	15	stat	40?	32

TABLE III.—REACTIONS TO INSULIN OF 24 PATIENTS IN RELATION TO THE DOSAGE OF INSULIN.

Insulin dosage (units).	Time between administration of insulin and reaction (minutes).	Blood sugar before administration of insulin (mg. per 100 cc.).	Blood sugar at time of reaction (mg. per 100 cc.).	Age of patient (years).
5	10	133	61	9
10	55	194	52	59
10	75	405	66	11
10	60	153	55	50
12	20	222	110	32
15	stat	40	40?	32
16	2	191	147	9
18	5	141	58	46
20	65	175	83	55
20	60	104	41	45
20	9	287	285	14
20	10	288	202	14
20	30	179	122	47
20	15	384	340	12
20	60	400	186	51
20	60	197	62	55
20	95	167	57	36
20	5	196	125	50
30	45	102	51	32
30	25	410	394	12
31	90	236	67	57
32	120	184	65	66
42	30	93	59	22
56	8	286	246	34

TABLE IV.—REACTIONS TO INSULIN OF 24 PATIENTS IN RELATION TO TIME BETWEEN THE ADMINISTRATION OF INSULIN AND THE REACTION.

Time between administration of insulin and reaction (minutes).	Insulin dosage (units).	(Blood sugar before administration of insulin (mg. per 100 cc.).	Blood sugar at time of reaction (mg. per 100 cc.).	Age of patient (years).
120	32	184	65	66
95	20	167	57	36
90	31	236	67	57
75	10	405	66	11
65	20	175	83	55
60	20	400	186	51
60	10	153	55	50
60	20	197	62	55
60	20	104	41	45
55	10	194	52	59
45	30	102	51	32
30	42	93	59	22
30	20	179	122	47
25	30	410	394	12
20	12	222	110	32
15	20	384	340	12
10	5	133	61	9
10	20	288	202	14
9	20	287	285	14
8	56	286	246	34
5	20	196	125	50
5	18	141	58	46
2	16	191	147	9
stat	15	40	40?	32

TABLE V.—REACTIONS TO INSULIN OF 24 PATIENTS IN RELATION TO BLOOD SUGAR VALUE AT TIME OF REACTION.

Blood sugar at time of reaction (mg. per 100 cc.).	Insulin dosage (units).	Time between administration of insulin and reaction (minutes).	Blood sugar before administration of insulin (mg. per 100 cc.).	Age of patient (years).
394	30	25	410	12
340	20	15	384	12
285	20	9	287	14
246	56	8	286	34
202	20	10	288	14
186	20	60	400	51
147	16	2	191	9
125	20	5	196	50
122	20	30	179	47
110	12	20	222	32
83	20	65	175	55
67	31	90	236	57
66	10	75	405	11
65	32	120	184	66
62	20	60	197	55
61	5	10	133	9
59	42	30	93	22
58	18	5	141	46
57	20	95	167	36
55	10	60	153	50
52	10	55	194	59
51	30	45	102	32
41	20	60	104	45
40?	15	stat	40	32

TABLE VI.—REACTIONS TO INSULIN OF 24 PATIENTS IN RELATION TO AGE.

Age of patient (years).	Insulin dosage (units).	Time between administration of insulin and reaction (minutes).	Blood sugar before administration of insulin (mg. per 100 cc.).	Blood sugar at time of reaction (mg. per 100 cc.).
9	5	10	133	61
9	16	2	191	147
11	10	75	405	66
12	30	25	410	394
12	20	15	384	340
14	20	10	288	202
14	20	9	287	285
22	42	30	93	59
32	30	45	102	51
32	12	20	222	110
32	15		40	40?
34	56	8	286	246
36	20	95	167	57
45	20	60	104	41
46	18	5	141	58
47	20	30	179	122
50	10	60	153	55
50	20	5	196	125
51	20	60	410	186
55	20	65	175	83
55	20	60	197	62
57	31	90	236	67
59	10	55	194	52
66	32	120	184	65

Conclusions. 1. The response to the administration of uniform doses of insulin varies considerably in the same and in different patients, under uniform conditions as to diet, and as to the relation of the time of administration to the ingestion of food.

2. The occurrence of a reaction after the administration of insulin apparently bears no uniform relation (*a*) to the size of the dose or (*b*) to the blood-sugar level.

3. The length of time between the administration of insulin and the occurrence of a reaction varies from an immediate response to several hours.

4. An exceedingly large dosage of insulin may not be followed by any reaction as is evidenced by the daily administration of 200 units (in two doses) to a six year old child for a period of one month without the occurrence of a single reaction.

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ON THE AMPHOTROPIC EFFECTS OF DRUGS UPON THE VEGETATIVE NERVOUS SYSTEM AND ON THEIR PHYSIOLOGIC AND CLINICAL SIGNIFICANCES.

By Eugene Baráth, M.D.

(From the Department of Internal Medicine (Clinic No. III) of the Hungarian Royal "Pázmány Péter" University in Budapest.)

A fundamental conception of the functions of the vegetative nervous system is based on the antagonistic relation existing between the two parts of this regulating system, the sympathetic and the vagus. Assuming this antagonism of the two systems, the normal and undisturbed functions of various organs can be imagined only in case the actions of both sympathetic and vagus system are in balance. This sharply expressed antagonism was chiefly maintained by Viennese pharmacologists, who stated that the effects of drugs which are able to influence the vegetative nervous system are sharply elective; thus adrenalin excites, for example, only the end apparatus of the sympathetic; pilocarpin the vagus system; while atropin has an inhibitory action on the functions of the latter (pharmacologic antagonism). Starting from this sharply expressed antagonism of the vegetative drugs, Eppinger and Hess built their well-known theory of vagotonia and sympathicotonia, the experimental proof of which, however, has thus far failed. This was due, among other reasons, to the fact that the examination of the vegetative nervous system was made mainly by means of drugs. The sharply elective effect of these drugs is by no means ascertained, as Lewandowsky asserted many years ago. At the time when the use of these drugs for the examination of the vegetative nervous system was beginning, many paradoxical reactions were observed, which showed that under certain circumstances these drugs may have other attacking points than those allowed by this theory. Among such paradoxical effects were considered the slowing of the pulse rate, the lowering of the blood pressure after the injection of adrenalin, the slowing of the pulse rate following the administration of atropin and many others. Slowing of the pulse rate, which must be expected according to theoretical considerations after pilocarpin, was very seldom observed.

Even the results of experiments on animals proved that injections of the vegetative drugs can be followed at the same time by symptoms of vagal and sympathetic excitement or paralysis. In recent years the investigations of many authors demonstrated that such double, or to use another word, *amphotropic*, effects of the vegetative drugs may be observed without doubt also on men. Being of great importance in functional pathology and therapy, it becomes necessary to analyze these paradoxical reactions. Under

what circumstances they appear must be investigated; it is a question whether they may be considered as really double effects upon the vegetative nervous system.

The literature of this problem is very large; and it is not our purpose to review it. We shall, however, attempt to give a description of the mechanism of this phenomenon, chiefly based on our own experiments. As a sample of an amphotropic vegetative effect we may give the effect of calcium which, as we have described it, manifests itself in an excitement of both parts of the vegetative nervous system. Let us shortly review the mechanism of this double effect.

According to the theory of Kraus and Zondek, we must admit that the effect of calcium is analogous to an alteration of the sympathetic; after the injection of calcium we should therefore observe only signs of sympathetic excitement. Instead, one may observe the following symptoms: Immediately after the injection of 5 or 10 cc. of a 10 per cent solution of calcium chloride we find a remarkable slowing of the pulse rate, which may amount to as much as 15 to 35 beats per minute; the oculocardiac test (eyeball-pressure test: Aschner) becomes decidedly positive. Both these phenomena indicate an excitement of the vagus system of the heart. Blood pressure shows often after an initial depression, a slight increase; the pupils get smaller. All these symptoms have a short duration. After five to ten minutes the initial slowing of the pulse rate disappears, the previous pulse rate is reëstablished and often it becomes even a little higher. The value of the blood sugar rises a little in the following one to two hours. The pupils get wider, the oculocardiac test becomes negative. Sometimes we find a positive adrenalin mydriasis test, as a sign of sympathetic excitement.

The effects of the calcium, as we have demonstrated it, cannot be taken as the result of pure sympathetic excitement. If we attempt to analyze the characteristic calcium bradycardia we find as follows: when 0.5 mg. of atropin sulphate is injected before the administration of calcium the slowing of the rate is missed. When 0.1 to 0.2 mg. of atropin are given intravenously at the summit of the calcium bradycardia, the bradycardia will disappear at once. We miss also the slowing of the pulse rate after bulbus pressure. (See Figs. 1, 2 and 3.)

All this proves that the calcium bradycardia is connected with the functioning of the vagus apparatus of the heart. The other symptoms, such as the increase of the blood sugar and blood pressure and the occasional positive adrenalin mydriasis test, show on the other hand an excitement of the sympathetic system. On the basis of these facts we can maintain that *the effect of calcium on man is manifested in a double reaction;* in the initial period there are strongly expressed symptoms of vagus excitement of short duration and these are followed by a less strongly expressed period of sympathetic

excitement with longer duration. A paper of Billigheimer, which has since appeared, confirms the correctness of these views.

The two phases of the calcium effect can be modified under certain circumstances. Thus we often missed the initial slowing of the pulse rate in many cases of exophthalmic goiter or it was less strongly expressed, and instead an acceleration of the pulse rate manifested itself. In these cases the effect of the oculocardiac test can be reversed; pressure on the eyeball brings about an increase of the pulse rate.

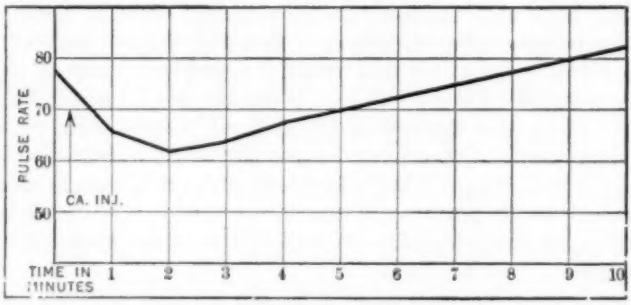

FIG. 1

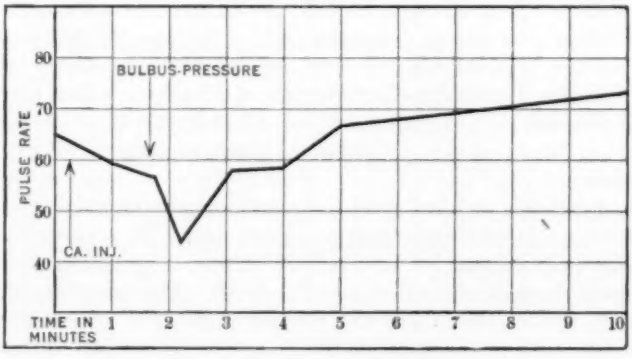

FIG. 2

The effect of calcium can be taken as the type for the obligate double effect on the vegetative nervous system. There are on the other hand some drugs which show such amphotropic effects only under certain circumstances; for example, atropin. The initial slowing of the pulse rate following the injection of atropin is well known. Petzetakis stated that in many experiments atropin nearly always produces such amphotropic effects; this depends, however on the dosage of the drug. After small doses there are signs of vagus excitement; only the largest doses produce an inhibi-

tory action on the vagus system. The recent investigations of Baley gave similar results and Danielopolu and his collaborators called attention many years ago to the double effect of pilocarpin and eserin.

Paradoxical effects can be observed also after the administration of adrenalin, although it has most typically an elective sympathetic effect, as has been already mentioned in the introduction of this paper. This paradoxical effect manifests itself in a slowing of the pulse rate and depression of the blood pressure as often observed in man in the initial period of adrenalin effect. In our experiments we have been able to observe a paradoxical effect of adrenalin on the blood-sugar value as follows: When giving adrenalin in small doses intravenously, we find usually a marked increase in blood pressure and blood-sugar values. When the small dose of 0.02 to 0.01 mg. are given, this increase of blood sugar is very slight or may be entirely missed. Often however we find even a remarkable diminution of blood sugar, chiefly in elderly men; this decrease amounts to from 20 to 40 per cent of the former value. Notwithstanding the effect of the adrenalin, increasing the blood pressure remains unchanged. (See Fig. 4.)

Therefore we have in these cases the peculiar fact that without the hyperglycemic effect of adrenalin or even with a hypoglycemic effect, the pressor effect is maintained: that is, *the hyperglycemic and pressor effects are dissociated. In these cases when an increase of the blood pressure is associated with a decrease of the blood-sugar level in the experiments, we may assume an amphotropic effect of the adrenalin,* because a characteristic sympathetic effect (increased blood pressure) is associated with an effect antagonistic to the usual effect on blood sugar, probably a parasympathetic effect (hypoglycemia).

The examples we have given are convincing enough that the effects of the vegetative drugs thus described must be regarded as true amphotropic vegetative effects. It is now a question of how to interpret these double effects of the drugs. One may suppose that these inverted effects are the proper expression of compensating processes, such as for instance the hyperglycemic effect of the adrenalin is always followed by an hypoglycemic stage. Against this interpretation is to be opposed that these inverted effects of the drugs often precede the usual reactions, as manifested for example by the initial blood pressure depressing and the slowing of the pulse rate after the injection of adrenalin. On the basis of animal experiments, it must be assumed that central reflex processes are also concerned in the mechanism of the drug effects on the vegetative system; these may be perhaps regarded as compensating reactions. Dresel and Billigheimer suggest that these phenomena are the expressions of amphotropic effects with compensating tendencies. According to their way of thinking, the two parts of the vegetative

nervous system are antagonistic merely in the effects produced; regarding the method of production they are synergistic; the sympathetic and the vagus are mutually influenced one by the other in that the excitement of the one is followed by a reactive excitement of the other system. This mutual interacting influence of the two systems is the basis for the normal functions of the organs. We are inclined to think it possible, however, that all the drugs

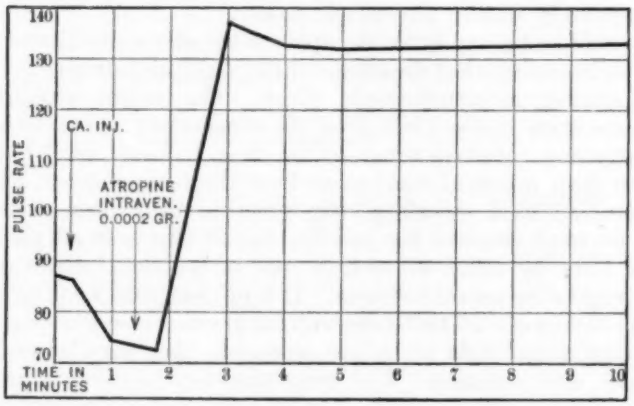

FIG. 3

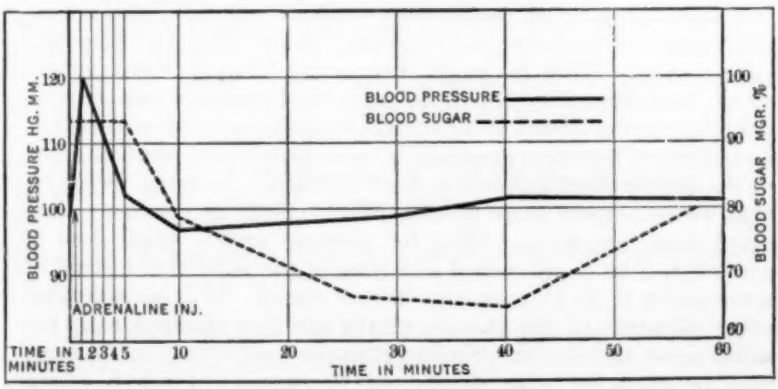

FIG. 4

acting on the vegetative nervous system are amphotropic substances; the resultant effects depend only on the doses administered and on the state of irritability of the functioning organs.

Very similar and analogous to the interpretation we have given to the diphasic drug effects is the recent theory of H. Zondek and Ucko upon the diphasic effects of hormones. They suggest that

the effect of hormones always appears in two phases, represented by two antagonistic processes. They are therefore, one may suppose, the mirror picture one of the other. So for example the hypoglycemic reaction after the administration of insulin is followed regularly by an hyperglycemic stage which must be considered, as the authors assert, as an active effect of the insulin. These diphasic hormonal effects may be analyzed only in series examinations and they occur ordinarily after the administration of approximately smaller physiologic doses.

We could add many other examples to the above-mentioned data which demonstrate that the effects of the vegetative drugs can often be considered as amphotropic effects. One might attempt to formulate some biologic law from the antagonistic effects of small and large doses of these drugs. Clinicians, however, have but the duty to draw practical conclusions from their experiments. From the facts we have described, two practical consequences follow: First, we must consider the possible double effects in all pharmacologic tests, by which we seek to analyze functional disturbances of the vegetative nervous system. It is obvious that we may interpret the results of such tests only with the greatest reserve, because—exact dosage and right technique supposed—they may be modified by many circumstances. The great tendency of decentralization existing in the organism and the various regulation of the organ functions allow us to consider the effects of the vegetative drugs as very complicated processes.

The other practical consequence to be drawn from the above-mentioned facts is that the vegetative drugs which are generally employed may afford in certain doses a very different, even contrary effect, from what is expected. According to Petzetakis and Danielopolu's view, the effects of all vegetative drugs must be regarded as amphotropic; but when greater doses are administered, the first phase of the double effect has only a short duration. It seems, therefore, that we can expect these unusual effects chiefly in the cases when small doses are given. Thus for example such a small dose of atropin as $\frac{1}{4}$ to $\frac{1}{3}$ mg. caused a slowing of the pulse rate instead of accelerating it, as Dawson and Bulmer stated. It is possible that other elements of the atropin effects are also changed with the small doses mentioned. Similar examples, important in therapy, may be given for other drugs; but we cannot enter into a long discussion of these paradoxical phenomena. The problems considered in this paper are scarcely to be considered as solved, as they are bound up with the difficult question of individual drug sensibility. The clearing up of these problems remains an object for experimental clinical pharmacology.

Summary. Evidence is given that the drugs attacking the vegetative nervous system may have often amphotropic (double)

effects; at the same time or successively they attack the sympathetic and the vagus.

The amphotropism of calcium and adrenalin is demonstrated.

Practical consequences of these effects are emphasized.

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THE ALLEGED ANTHELMINTIC PROPERTY OF QUISQUALIS INDICA (SHIH CHUN TZE), WITH CASE REPORTS.

By K. K. Chen, Ph.D.,

AND

Hsiang-chuan Hou, M.D.,

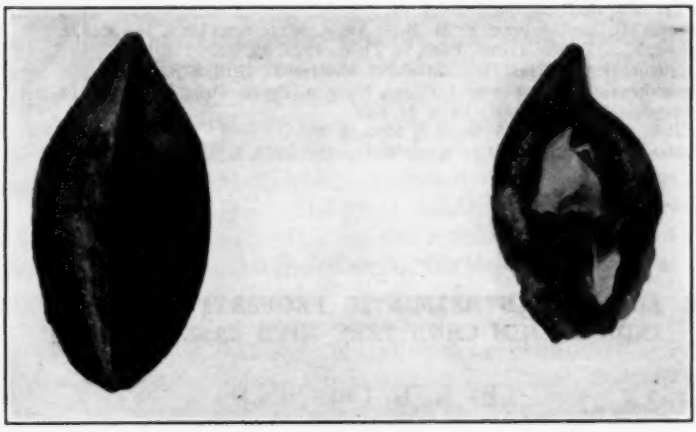
PEKING, CHINA.

(From the Departments of Pharmacology and Medicine of Peking Union Medical College, Peking, China.)

The drug Shih Chun Tze, or Quisqualis indica, fam. Combretaceæ, has long been known in China as a powerful anthelmintic.[1] Modern literature appears to accept this belief[2] and to confirm its efficacy. Thus Davenport,[3] in 1918, reported his success with the drug in the treatment of ascariasis, but not in ankylostomiasis or other infestations of the intestine. In the spring of 1924, we were encouraged by Dr. Montgomery of Chunchowfu near Amoy to undertake this investigation. In speaking of his good results in ascariasis, Dr. Montgomery proceeded, ". . . If you can discover the active principle and work out a concentrated form, I believe we have a

real substitute for santonin. The native doctors use it extensively and find it effective." The present paper is to report our experience with this drug in ascariasis. The results of our phytochemical study will be published elsewhere.

The drug is sold by the Chinese drug stores in the form of nuts. It is spindle-shaped (Fig. 1, *A*), brown, about 3.5 to 4 cm. long and 1.7 to 2 cm. in the greatest diameter, and has five ridges, almost equidistantly arranged, running from one pole to another. Midway between two adjacent ridges, there is a depression joining both poles. When the shell is opened, a yellowish dicotyledonous seed is found inclosed in a brownish-black adherent seed-coat (Fig. 1, *B*). It is this kernel that is believed to have the anthelmintic action. The best seeds are produced in Fukien Province and Dr. Montgomery



A *B*

FIG. 1.—The nuts of Quisqualis indica. *A*, Whole; *B*, opened.

kindly sent some of this type, together with his letter. The constituents obtained by us were a fatty oil, a gum, sugars, potassium sulphate, and calcium sulphate. The gum was the only principle among them that showed chemical complexity and thus might exhibit some pharmacologic activity. Our study in animals and in men was limited to the gum, and then the whole kernel, in order to be certain that no other active principle was overlooked, which could not be easily separated by chemical means.

Results in Dogs. Our first object was to determine, roughly, the toxicity. Puppies of 3 to 4 kilos, when given orally 1 to 1.5 gm. of the ground seed, showed no untoward symptoms. The isolated gum suspended in water, or the concentrated infusion prepared from the seed, invariably caused drowsiness and vomiting. These animals recovered completely within ten hours. An emulsion of

the fatty oil, isolated from the seed, produced purgation. The drug therefore has a low toxicity.

Next we made four observations—two with the gum and two with the crude powdered seeds—in two puppies infected with Ascaris mystax. The drug was dispensed in capsules and given by mouth. The largest dose was equivalent to four seeds. Each dose was preceded an hour before, and followed three to four hours later, by 2 teaspoonfuls of magnesium sulphate. In none of these experiments was there any worm expelled with the feces.

Results in Men. The negative results in canine ascariasis were not necessarily proof of the inactivity of the drug in human ascariasis, for the infecting agent in men is of a different species (Ascaris lumbricoides). According to the Chinese custom, the seeds are baked and eaten like peanuts. Davenport[3] used the baked and pulverized kernels. We made 13 observations in 11 cases—3 with the gum, 6 with the raw, and 4 with baked seeds (all pulverized). The dosage per capsule of gum was 0.16 gm., of the raw seed 0.57 gm. (equivalent to 1 seed), later increased to 0.82 gm., and of baked seed 0.88 gm. (equivalent to 1½ seeds). A course of treatment consisted of light diet for twenty-four hours followed by a dose of magnesium sulphate, then by 4 capsules (1 every three hours), and again by a dose of magnesium sulphate. The number of capsules was later doubled. The largest total dose in a single course was 7.04 gm. (equivalent to 12 seeds) which caused vomiting in a patient. All stools were examined for worms during the following two or more days, and for ova for four to seven days immediately after the treatment.

Ten of the 13 observations showed no improvement from the infection. Each of the 3 other patients expelled an adult worm following the course. Two of these patients were positive for Ascaris ova by repeated examinations, while the third showed the absence of ova in a single examination. No second specimen was obtainable from the last individual after the discharge from the hospital. It was most likely that the worms expelled in these cases were mechanically carried out by the saline cathartic. The overwhelming majority showed the presence of ova (12 out of 13), indicating that Quisqualis indica is practically useless in the treatment of ascariasis.

Three of the patients finally received 0.8 cc. of oil of chenopodium together with 1.5 cc. of carbon tetrachlorid followed by a saline cathartic. One of them passed 2 adult worms while the other two showed no response. Repeated microscopic examination of stools showed uniform absence of Ascaris ova during the week following. The contrast of therapeutical value between oil of chenopodium and carbon tetrachlorid, on one hand, and Quisqualis indica on the other, is therefore obvious.

Case Abstracts. CASE I.—A man, aged twenty-nine years, was admitted to Peking Union Medical College Hospital for enlarged spleen and liver with ascites. The patient appeared to be emaciated and moderately ill. Stool examination was positive for Ascaris ova. Primary diagnosis was not definitely established at the time of our study. The patient was given a course of treatment with the gum (0.68 gm. in 4 doses). No worms were recovered from the stools. Microscopic examination of the stools passed on the fourth and fifth day showed the presence of Ascaris ova. The patient was finally given a mixture of oil of chenopodium (0.8 cc.) and carbon tetrachlorid (1.5 cc.) in a capsule, followed an hour later by 30 cc. of saturated solution of magnesium sulphate. Two adult worms were passed in the night following. Stool examinations on the fifth and sixth day were negative for Ascaris ova.

CASE II.—A woman, aged twenty-three years, was admitted to Peking Union Medical College Hospital for the fracture of the neck of femur. Stool examination was positive for ova of Ascaris lumbricoides. The patient was given a course with the raw kernels, the total amount being 2.85 gm. in 5 doses. On the fourth and fifth day after the treatment, stool examination still showed the presence of ova. Four days later, she was given a second course, now with the baked kernels, the total dose being 7.04 (equivalent to 12 seeds). One adult Ascaris worm was passed in the night of the following day. Microscopic examinations of stools on the fourth, sixth, and seventh day were all positive for Ascaris ova.

Cases III to XI were essentially the same, except that 1 case after the administration of raw kernels showed the absence of Ascaris ova on a single stool examination. Two cases after the administration of oil of chenopodium, together with carbon tetrachlorid, were both free from ova in stools on repeated examinations, while a previous course of Quisqualis indica had no influence over the infection.

Conclusions. Neither the gum isolated from the seed, nor the whole seed (raw or baked) of Quisqualis indica, has any anthelmintic action for ascariasis.

NOTE.—We wish to express our thanks to Dr. Montgomery of Chunchowfu for his gift of our material for study, to Prof. E. C. Faust for his coöperation in the study of canine ascariasis, and to Prof. O. H. Robertson for his encouragement in the clinical study.

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THE USE OF LIPIODOL IN THE LOCALIZATION OF SPINAL LESIONS.

II. The Local and Systemic Effects of the Injection of Lipiodol into the Subarachnoid Space.

By Franklin G. Ebaugh, M.D.,

and

Hugo Mella, M.D.,

Denver, Colo.

(From the Colorado Psychopathic Hospital, Medical Department, University of Colorado.)

Since the introduction of the use of lipiodol by Sicard[1] many articles have appeared in both American and foreign literature,[2, 3, 4, 5, 6] proving conclusively the diagnostic value of this oil for the localization of spinal subarachnoid block. All observers agree that lipiodol should only be used to supplement careful preliminary neurologic examination, to make an accurate localization for the neurologic surgeon. Mixter[4] especially emphasizes the need for the complete neurologic examinations.

The object of this study is to determine the following:

1. The local effects of the injection of lipiodol—mainly the duration of aseptic meningitis, if any is present, as determined by the spinal-fluid cell changes, quantitative protein determinations and any irritative phenomena found in the report of the neurologic examinations following injection.

2. The general systemic effects of the injection.

3. The length of time required for lipiodol to pass from cisterna magna to the lumbar sac and to determine if any lipiodol is held back by the posterior roots, folds or pockets of the arachnoid, thereby leading to an inaccurate diagnosis of subarachnoid block. To note any evidence of inflammatory changes which may have caused arachnoid adhesions or obliteration of the subarachnoid space through thickening of the meninges about the spinal cord in paresis.

Type of Cases and Method of Study. Thirteen patients were used in this study; 5 typical cases of general paresis, 3 cases of multiple sclerosis, 2 with histories of old back injuries and the remaining 3 with evidence of degenerative neurologic lesions. While lying on his side each patient was injected in the cisterna magna with 2 cc. of lipiodol. Then the patient sat up immediately and Roentgen ray examinations were made of the cervical, dorsal and lumbar regions. These roentgenographic studies were repeated in six hours, twenty-four hours and seven days after the injection. Blood counts

were likewise taken. Complete examinations of the spinal fluid were made at the above intervals, consisting of cell count, quantitative protein examination and the colloidal-gold reaction. The patients were kept in bed in a sitting position for one week. The laboratory data is arranged in the following table, showing conclusively that definite findings of meningeal irritation were present (Chart I).

A brief résumé of each case, along with characteristic roentgenograms are as follows:

Case Reports. CASE I.—W. K., male, aged forty-nine years, was admitted to the hospital, July 7, 1925, with a history of irritability and of grandiose delusions. Spinal fluid and blood Wassermanns, positive; colloidal-gold curve, 5555554000. Diagnosis, general paresis.

Injection of 1 cc. lipiodol on August 11. Patient complained of no physical discomfort following injection, and his temperature remained normal. No loss of sleep. Leukocyte count before injection, 10,100; twenty-four hours after injection, 9600.

CASE II.—(Fig. 1.) J. C., male, aged forty-four years, was admitted to the hospital, August 6, 1925, complaining of failing sight, beginning about six months previous to admission. Blood Wassermann questionable; spinal fluid Wassermann, 4–4; gold curve, 5555555540; bilateral optic atrophy. Diagnosis, general paresis.

Injection of 1 cc. lipiodol made on August 12. Reaction marked. For three days following injection patient's temperature varied from 99.2° to 101° F., and patient complained of backache. On the fourth day his temperature returned to normal and he had no further physical complaints. Leukocyte count before injection, 6400; twenty-four hours after injection, 9400.

CASE III.—L. M., male, aged thirty years, was admitted to the hospital, May 8, with loss of memory, overactivity, overproductivity and irritability. Blood Wassermann questionable; spinal fluid Wassermann, 4–4; gold curve, 4455543000. Diagnosis, general paresis.

Injection of lipiodol on August 13, 1925. Patient complained of no discomfort following injection. Temperature went to 100° F. day after injection, but returned to normal on second day. Leukocyte count before injection, 8000; twenty-four hours after, 5400.

CASE IV.—J. O., female, aged fifty years, was admitted to the hospital, June 30, 1925, with complaint of pain and weakness in back, smarting of eyes and twitching of eyelids and general weakness. History of syphilis. Blood and spinal fluid Wassermanns

FIG. 1.—(Case III.) Typical picture of lumbar sack, showing how lipiodol has descended to this region.

FIG. 2.—(Case III.) Showing lower thoracic and lumbar spine of same case. This is characteristic of all our cases showing no block.

FIG. 3.—(Case X.) Fracture with dislocation of the first, second and third cervical vertebræ, showing retention of a small amount of lipiodol just below the foramen-magnum and thin strip at level of third and fourth cervical vertebræ.

FIG. 4.—(Case X.) Ninety-six hour plate. Shows lipiodol has passed the block.

FIG. 5.—(Case XIII.) Shows retention of small amount of lipiodol and point of greatest curvature.

FIG. 6.—(Case X.) Shows arrest of lipiodol at the posterior roots of the second, third, fourth and fifth lumbar vertebræ.

both positive; gold curve, 5554310000. Diagnosis, general paresis.

Injection of lipiodol on August 15. No pronounced reaction. Patient complained of feeling "tired" the day after injection and on the fourth day complained of being "stiff and sore." No increase in temperature. Leukocyte count before injection, 5000; twenty-four hours after, 10,000; five days after, 8800.

CASE V.—M. D., female, aged forty-two years, was admitted to the hospital, July 25, 1925, from outside county. No history given. Patient complained of headache; was delusional and irritable. Blood and spinal fluid Wassermanns positive; gold curve, 44555432000. Diagnosis, general paresis.

Injection with lipiodol on August 17. On August 18 the patient complained of severe pain in right hip. Did not sleep well that night and the next day, August 19, complained of pain in back and hips. Slept well that night and had no complaints on the third day. Leukocyte count before injection, 5600; five days after, 4000 (Fig. 4).

CASE VI.—(Fig. 5.) W. E., male, aged fifty years, was admitted, August 17, 1925, complaining of difficulty in walking and occasional tremor in hands. History of several severe accidents involving injuries to back and head. Diagnosis of multiple sclerosis without psychosis made.

Lipiodol injected on August 20. Temperature on August 21, 101.6° and 101° F.; normal on August 22 and 23. Patient complained of headache and soreness in legs on August 21. On August 22 had backache, headache and increased pain in legs. On August 23 patient complained of a little headache but of no other discomfort. No disturbance of sleep. Leukocyte count before injection, 6400; twenty-four hours after, 8400.

CASE VII.—G. M., male, aged thirty-five years, was admitted, September 6, 1925, with history of difficulty in walking, extreme irritability and depression followed by restlessness and overproductivity. Illness developed after attack of influenza in 1918. Serology negative; gold curve normal. Diagnosis of multiple sclerosis. Psychiatric picture on admission was that of hypomanic reaction.

Injection of lipiodol on August 16. No reaction. Temperature remained normal; sleep undisturbed; no physical discomfort. Leukocyte count before injection, 7050; count not made after injection.

CASE VIII.—M. H., male, aged forty-seven years, was admitted to the hospital, September 20, 1925, with history of paranoid delusions about wife and children. Had had operation for ptosis of stomach six years before, followed by weakness and constant com-

plaints about health. History of neck injury followed by severe pain in right lumbar region, nausea and loss of strength. Question of possible cord injury.

Lipoidol injection was made on October 15. Patient made some complaints of pain in back following injection. However, patient was hypochondriacal during entire stay in hospital and complaints after injection were no more numerous than at any other time. No loss of sleep. No rise in temperature. Leukocyte count before injection, 13,200; twenty-four hours after, 7800.

CASE IX.—J. M., male, aged forty-five years, was admitted, November 21, 1925, with complaint of dull ache in back, loss of strength and incapacity for work. Diagnosis probably multiple sclerosis. Spondylitis deformans.

Injection of lipiodol on November 23. Temperature normal on November 23 and 24; went to 100° F. on morning of November 25 and again on November 26; temperature normal on November 27. Patient slept poorly for two nights following injection and complained of pain in legs until November 27. No permanent ill effects. Leukocyte count before injection, 6050; twenty-four hours after, 5700.

CASE X.—D. M., male, aged forty-five years, was admitted, November 11, 1925, with complaint of numbness in legs and hands present for approximately eighteen months with staggering gait at times. Legs more affected than hands. History of severe injury to head in 1904. Patient unable to lift head for several days following accident. Diagnosis of old fracture of first and second cervical vertebræ with cord injury. Blood Wassermann questionable; spinal fluid Wassermann negative; gold curve normal.

Injection of 2 cc. lipiodol on November 20. Temperature, November 20 to 24 varied from 98° to 101.2° F.; returned to normal on November 24. Patient slept poorly the first night but lost no sleep on succeeding nights. Complained of no pain (Fig. 6).

CASE XI.—J. M., male, aged fifty-two years, was admitted on August 1, 1925, with complaint of pain in left leg, loss of weight and eruption on forehead over each eye. History of syphilis at twenty-five years and of heavy drinking before enactment of prohibition. Spinal fluid Wassermann negative; gold curve normal. Diagnosis made of cerebral arteriosclerosis and intermittent claudication.

Injection of lipiodol on September 1. Temperature before injection was 100.2° F.; went to 100.8° F. after injection but returned to normal on September 3. Patient complained that the pain in his leg was worse following the injection, but this lasted only a few hours and on the day after injection he had no complaints. Slept poorly the night after injection. Leukocyte count before injection, 5600; twenty-four hours after, 9200.

CASE XII.—E. W., female, aged twenty-nine years, was admitted, November 20, 1925. History of sudden onset of paralysis in September, 1912. Legs completely paralyzed below hips. Contracture of legs and ankles. Patient was acutely ill for eight months following onset of paralysis. Has had chronic headaches since. Very depressed since February, 1925, and was admitted as emergency case owing to suicidal inclination. Residual from polioencephalitis. Question of possible injury to spine.

Injection of lipiodol on December 7. Temperature normal following injection. Patient has extreme nausea and complained of headache. Also complained of some pain in legs and back for two days after injection. Slept well. Leukocyte count before injection, 10,900; twenty-four hours later, 8700.

CASE XIII.—J. B., female, aged twenty-nine years, was admitted, October 9, 1925, with complaint of marked change in disposition beginning four years previous to admission. Refused to mingle with people, showed fear of noises and refused to eat or talk at times. Laboratory findings negative. Patient showed marked scoliosis and kyphosis of spine.

Lipiodol injected on November 13. Patient was very nauseated but complained of no pain after injection. Temperature a few hours after injection was 100.8° F.; for three days temperature ranged from 99° to 100.8°; returned to normal on November 17. No loss of sleep. Leukocyte count before injection, 7650; twenty-four hours after, 13,500.

Summary of Local Effects of Injections and Laboratory Data. Chart I indicates definite evidence that an aseptic meningitis is produced following the introduction of lipiodol into the spinal subarachnoid space. These reactions, however, are of transient duration in that all cases tended to recover quickly within a period of three days. The cellular and globulin increase appears to be more severe in the paretic group than in the average case. The reaction in multiple sclerosis assumed an intermediate position between these two groups. The increase in the quantitative total protein above the increase in cellular response is of interest, especially in general paresis and multiple sclerosis, and demands further study. The duration of this increase in quantitative protein was not followed in this series, as the cases studied were in many instances only in the hospital for a short time. The occurrence of frequent bloody taps in lumbar puncture after injection appears to indicate a generalized congestion of the vessels. The possibilities of an actual hemorrhage in the subarachnoid space has not been noted by us in 5 cases previously studied who came to operation, and we do not feel that the frequent bloody taps were due to faulty technique.

Number of lumbar punctures made following injection with lipiodol, 34; number of bloody taps, 10 (27 per cent). Records on 50 lumbar punctures taken at random from hospital records show no bloody taps.

Systemic Effects. The general systemic effects following the introduction of 2 cc. of lipiodol into the spinal subarachnoid space summarized as follows: Pain in legs in 4 cases. Slight increase in temperature in 3 cases. Nausea and headache were present in Case XII, following lipiodol injection. The leukocytes were

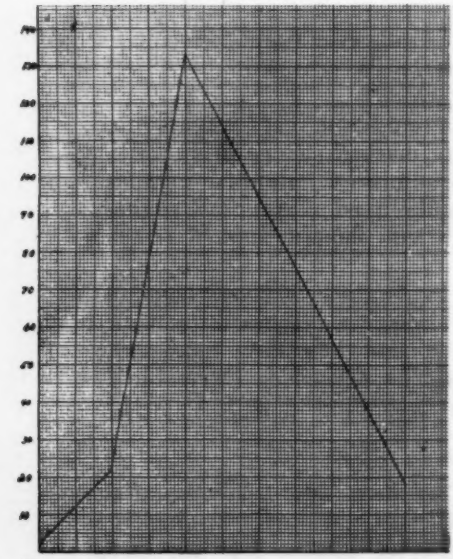

CHART I.—Average cell count of 13 cases after injection of lipiodol.

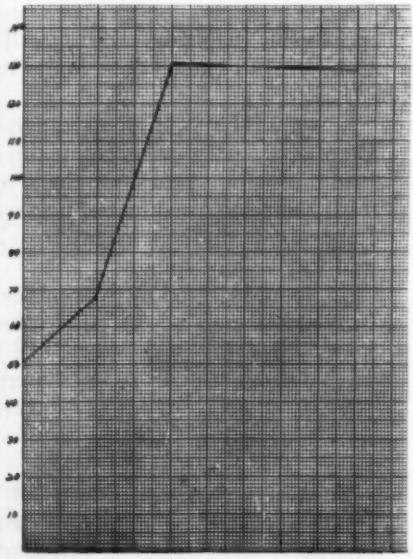

CHART II.—Average total protein of 13 cases after injection of lipiodol.

increased in only 4 cases, showing a decrease in 8 cases. The count was not taken after the injection on 1 patient. The sleep curve in several cases was affected, and many of the patients showed a general restlessness.

Is Lipiodol Held Back by Posterior Roots? In this group of 13 cases evidence was found to indicate that lipiodol was held back by the posterior roots in 2 cases, of which the enclosed roentgenogram (Fig. 6), in Case X, is characteristic. There was no evidence of any subarachnoid block in the 5 cases of general paresis. Lipiodol in Cases III and IV, in which there was no obstruction, reached the end of the lumbar sack a few seconds after injection.

Discussion. In the 13 cases studied there appeared to be no doubt but that the injection of lipiodol produced a fairly severe

aseptic meningitis, as indicated in the cellular increase in the spinal fluid and increases in quantitative protein, and the frequency of bloody taps. These changes have been previously emphasized in animal experiments by Ayer.[2] Although definite evidence of irritation of the spinal subarachnoid space is present, these changes are of transient duration and should not contraindicate the use of lipiodol to supplement preliminary neurologic examinations. However, Maclaire[7] reports a case operated upon in which lipiodol caused extreme irritation, leading to encystment in the subarachnoid space. In this case a mistake in the diagnosis of cord compression was made owing to kyphosis of the fourth dorsal vertebra and fusion of the fifth and sixth dorsal vertebræ leading to the arrest of lipiodol. The tendency for protein increase to continue to ten days demands further consideration. Likewise a study of the chlorid content of the spinal fluid should prove of value. The systemic effects noted in several cases likewise are transient and do not appear of sufficient severity to contraindicate the use of lipiodol. No prolonged subjective complaints or permanent residuals have followed this operation. Cases VIII and X show the value of lipiodol in demonstrating old spinal-cord injuries which readily accounted for the obscure neurologic findings.

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REVIEWS.

EMERGENCY SURGERY. By GEORGE DE TARNOWSKY, M.D., F.A.C.S., D.S.M. Pp. 718; 324 illustrations. Philadelphia: Lea & Febiger, 1926. Price, $7.50.

THIS volume deals with the question of emergency surgery as has been developed through the military surgery of the World War. The author adapts these principles to civil life. Many of the old-time principles and practices that has been proven to be antiquated have been left out of the various chapters. Those features that have a sound physiological, anatomical, as well as biochemical basis, are retained. The chapter on the emergency treatment of wounds is exceptionally good. The book is more than an emergency surgery; in fact it overlaps into a treatise on surgical conditions of a more or less general nature as evidenced by descriptions of skin graft, plastic operations of a secondary nature, operations for repairing of nerves, removal of neuromata, the treatment of empyema, etc. The book is richly illustrated and the vast majority of the illustrations are well worth while. My one criticism of the book is that less space should be given to classifications of conditions and more attention be paid to the actual technical handling of the various conditions.

E. E.

THE CLINICAL INTERPRETATION OF THE WASSERMANN REACTION. By ROBERT A. KILDUFFE, A.B., A.M., M.D., Director, Laboratories, Atlantic City Hospital; Consulting Serologist, Betty Bacarach Home for Children, Atlantic City, N. J.; City Bacteriologist, Atlantic City N. J. Pp. 203; 6 illustrations. Philadelphia: Lea & Febiger, 1926. Price, $2.50.

THIS book presents the serologist's evaluation of the Wassermann reaction based on a survey of the literature and on personal experience with the test. It should prove useful in promoting a better understanding between the clinician and the serologist.

J. S.

POSTMORTEM APPEARANCES. By JOAN M. ROSS, M.B., B.S. (LOND.), M.R.C.S., L.R.C.P., Assistant Pathologist to St. Mary's Hospital. Pp. 198. London: Humphrey Milford, Oxford University Press, 1925.

THE title of this volume suggests slate-writing and nebulous photography, but further examination might disappoint a disciple of Lodge and Doyle. This manual should fill a real need in the demands of the general practitioner and medical student for brief descriptions of the gross morbid changes in the human body due to disease. Some passages of English origin might prove unusual or obscure to an American, such as "hot-cross bun head." However, the book will be found authoritative, and the material shows careful selection. M. B.

DISEASES OF INFANTS AND CHILDREN. By HENRY DWIGHT CHAPIN, A.M., M.D., Emeritus Professor of Medicine (Diseases of Children) at the New York Post Graduate Medical School and Hospital, and LAWRENCE THOMAS ROYSTER, M.D., Professor of Pediatrics and Head of the Department of Pediatrics, University of Virginia. Fifth revised edition, Pp. 633; 163 illustrations, 11 colored plates, and numerous charts and tables in the text. New York: William Wood & Co., 1925. Price, $6.00.

THIS textbook is a fifth edition of the former work of Chapin and Pisek, the death of the latter requiring a new collaborator. It is an attractively assembled book, clearly printed on good paper, and excellently illustrated, orderly in arrangement and accurate in statement. Compactness has been attained by the authors with some sacrifice of detail, especially in the subject of infantile digestive disorders. A handy table of drug dosages at different ages, a compact list of diets for after the first year, a diagnostic table of the exanthemata, a weight-height chart, a practical table of food values will make the work a handy desk volume for the practitioner. As a whole the subject of pediatrics has been well covered, but brief consideration of rabies and roseola infantum would add to its completeness. J. S.

INFECTION, IMMUNITY AND INFLAMMATION. By FRASER B. GURD, M.D., C.M., F.A.C.S., Lecturer in Applied Immunology and in Surgery, McGill University, Montreal. Pp. 321. St. Louis: The C. V. Mosby Company, 1924.

THE known facts about infection, immunity, inflammation and methods of their treatment are set forth in this volume in an inter-

esting and pleasing manner. The practical aspects of the subject, based upon the experiences and opinions of the author, should enhance its value to the general practitioner.

Each subject is briefly reviewed before any attempt is made to attack the more difficult and complex. The questions treated are not of academic interest only, but also practical and useful. Instead of the usual lengthy presentation of "the method of performing" the Wassermann reaction, we find a thorough explanation of "what it is" and "what it means." Careful consideration is made of the phenomenon of anaphylaxis, with the hope of enabling the reader to understand its bearing upon infection, and to appreciate the nature of the "serum disease," and the sudden and sometimes fatal "anaphylactic shock."

There are no illustrations, for the book does not need them. Neither is there a lengthy bibliography, since the useful references are given as footnotes. The book should serve more as a guide than a reference, and will prove of more value when read consecutively and entirely than when occasionally looked into.

R. O.

A Textbook of Physiology. By William D. Zoethout, Professor of Physiology, Loyola University. Second Edition. Pp. 616; 186 illustrations. St. Louis: C. V. Mosby Company, 1925. Price, $4.50.

This book is designed for students in dental, pharmacy, and normal schools and has much to recommend it. The subject is treated briefly but clearly, and a number of excellent references are given to review articles and monographs dealing more elaborately with special topics. The facts are given with commendable accuracy and recognition of recent work, so that the book is up to date, and forms an admirable introduction to the subject. There is little to criticise, except, perhaps, to raise the question whether dental students should be permitted to study such a fundamental subject in such a concise form.

H. B.

Insects and Disease of Man. By Carroll Fox, M.D., Surgeon, U. S. Public Health Service. Pp. 249; 92 illustrations. Philadelphia; P. Blakiston's Son & Co., 1925. Price, $4.00.

This thoroughly practical work upon medical entomology, by an author who has had extensive experience in the United States Public Health Service, is intended for field health officers, physicians, entomologists, and students of public health. It contains in surprisingly small compass an immense amount of valuable material

otherwise difficult to find, and so arranged and indexed as to be immediately available for practical purposes.

Part I deals with medical entomology, and is structural and systematic. It makes difficult reading, but valuable matter. Nowhere have we seen more useful keys for the identification of noxious insects, or better descriptions of important species than here. After the careful perusal of Section XXIII, which deals with the technique of the subject, it seems to us that any intelligent person possessed of a good hand lens, ought to be able to identify any insect of medical importance.

Part II deals with the diseases of man transmitted by insects, and constitutes the chief readable part of the work. Here are to be found in brief form, the causative agent, source of infection, mode of transmission, period of incubation, communicability, epidemiology, symptomatology, and prophylaxis of malaria, yellow fever, dengue fever, filariasis, tularemia, bubonic plague, typhus fever, trench fever, relapsing fever, African sleeping sickness, and tsutsugamushi fever, with all of the latest information upon those interesting and important conditions. J. F.

CLINICAL DISORDERS OF THE HEART BEAT. A HANDBOOK FOR PRACTITIONERS AND STUDENTS. By SIR THOMAS LEWIS, M.D., F.R.S., Physician and Lecturer in Cardiac Pathology, University College Hospital, and so forth. Sixth Edition. Pp. 131; 55 illustrations. London: Shaw and Sons, 1925.

IN fifteen years this small book has passed through six editions—a just tribute to a valuable work by a leading authority in his field—and yet so well were laid the foundations of the new subject—cardiology—that the main outline of the work and most of the eight chapters have been preserved with but few essential changes. Auricular flutter now requires a chapter; and for auricular fibrillation the now familiar circus movement is explained and newer methods of therapy—digitalis and quinidin—are recommended. On the other hand, the presentation of premature contractions remains unchanged and in the chapter on heart block, even in a book of this size, one regrets omission of the statement that long continued complete block may occur without destruction of His' bundle.

Most important for the general reader, for whom this book is designed, are the few pages of preface in which the author sets in proper perspective the contributions of the graphic method to our knowledge of the heart and its diseases. E. K.

BOOKS RECEIVED.

The Diagnosis, Treatment and End Results of Tuberculous Disease of the Hip Joint. By GEORGE PERKINS, M.CH. (OXON), F.R.C.S. (ENG.). Pp. 118; 49 illustrations. New York: Oxford University Press, American Branch, 1926, Price, $1.75.

Proceedings of the Charaka Club. VOL. VI. Pp. 145. New York: Paul B. Hoeber, Inc., 1925. Price, $4.00. Entertaining essays from this well-known group of New York raconteurs.

Thomas Sydenham, Clinician. By DAVID RIESMAN, M.D. Pp. 52; 1 illustration. New York: Paul B. Hoeber, Inc., 1926. Price, $1.50. Reprinted from the Annals of Medical History.

Gastric Function in Health and Disease. By JOHN A. RYLE, M.D. Pp. 152; 28 illustrations. New York: Oxford University Press, American Branch, 1926. Price, $2.75.

Nervous and Mental Disorders from Birth through Adolescence. By B. SACHS, M.D., AND LOUIS HAUSMAN, M.D. Pp. 861; 110 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, $10.00.

Surgical Clinics of North America. February, 1926, VI, No. 1, Philadelphia Number. Pp. 325; 136 illustrations. April, 1926, VI, No. 2, San Francisco Number. Philadelphia: W. B. Saunders Company, 1926.

Emergency Surgery. By GEORGE DE TARNOWSKY, M.D., F.A.C.S., D.S.M. Pp. 718; 324 illustrations. Philadelphia: Lea & Febiger, 1926. Price, $7.50.

Disease Prevention. BY HERBERT H. WAITE, M.D. Pp. 667. New York: Thomas Y. Crowell Company, 1926. Price, $4.50.

Pediatrics. EDITED BY ISAAC A. ABT, M.D. VOL. VIII and Index. Pp. 1102 and 249; 388 illustrations. Philadelphia: W. B. Saunders Company, 1926. Price, $10.00 per volume. Review to follow.

The Principles and Practice of Endocrine Medicine. By WILLIAM NATHANIEL BERKELEY, PH.D., M.D. Pp. 368; 60 illustrations. Philadelphia: Lea & Febiger, 1926.

A Manual of Normal Physical Signs. By WYNDHAM B. BLANTON, B.A., M.A., M.D. Pp. 215. St. Louis: C. V. Mosby Company, 1926. Price, $2.50. It is doubtful if manuals in notebook form are proper aids to beginners. As a handy reference this book may be useful.

A Bipolar Theory of Living Processes. By GEORGE W. CRILE, M.D. Pp. 405; 62 illustrations. New York: The Macmillan Company, 1926.

Surgical Anatomy of the Human Body. VOL. I. Second edition. By JOHN B. DEAVER, M.D., SC.D., LL.D., F.A.C.S. Pp. 551; 124 illustrations. Philadelphia: P. Blakiston's Son & Co., 1925. Price, $12.00 per volume.

The Comparative Anatomy, Histology and Development of the Pituitary Body. By G. R. DE BEER, M.A., B.SC., F.L.S. Pp. 108; 129 illustrations. London: Oliver and Boyd, 1926. 12/6 net.

Textbook of Materia Medica for Nurses. By LAVINIA L. DOCK, R.N., and JENNIE C. QUIMBY, R.N. Pp. 317; 13 illustrations. 8th ed. New York: G. P. Putnam's Sons, 1926. Price, $2.25. Rewritten to conform with the 10th revision of the U. S. Pharmacopœia.

Collected Papers by the Staff of the Henry Ford Hospital. Pp. 634; 151 illustrations and 42 charts. New York: Paul B. Hoeber, Inc., 1926. Price, $8.00. A comprehensive collection of forty-nine articles covering most phases of modern medicine.

Advising the Tuberculous about Employment. By W. I. HAMILTON, and T. B. KIDNER. Pp. 171. Baltimore: Williams & Wilkins Co., 1926. Price, $2.00. Practical points of value in rehabilitating the tuberculous.

Manual of Bacteriology. By R. TANNER HEWLETT, M.D., F.R.C.P., D.P.H. (LOND.), F.K.C., F.R.M.S. Pp. 645, 101 illustrations. 8th ed. London: J. and A. Churchill, 1926.

Roentgen Interpretation. A Manual for Students and Practitioners. By GEORGE W. HOLMES, M.D., and HOWARD E. RUGGLES, M.D. Pp. 326; 226 illustrations. 3d ed. Philadelphia: Lea & Febiger, 1926. Price, $5.00. A valuable brief survey of Roentgen ray diagnosis properly emphasizing the necessity for a thorough knowledge of pathology and correlation with clinical and autopsy findings.

International Medical Annual. Pp. 555; 66 illustrations. New York: Wm. Wood & Co., 1926. Price, $6.00. A relatively excellent presentation by a good list of contributors.

Massage und Gymnastik im Dienste der Kosmetik. By DR. FR. KIRCHBERG. Pp. 99; 26 illustrations. Lepsic: Georg Thieme, 1926. Of limited interest but correspondingly valuable to those wishing information on this subject.

A Textbook of Urology. By OSWALD SWINNEY LOWSLEY, A.B., M.D., F.A.C.S., and THOMAS JOSEPH KIRWIN, PH.C., B.S., M.A., M.D. Pp. 699; 246 illustrations. Philadelphia: Lea & Febiger, 1926. Price, $10.00.

Modern Views on Digestion and Gastric Disease. By HUGH MACLEAN, M.D., D.Sc. Pp. 170; 37 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, $4.00.

Collected Papers of the Mayo Clinic, Rochester, Minnesota, 1925. Pp. 1078; 252 illustrations. Philadelphia: W. B. Saunders Company, 1926. Price, $13.00. Even more valuable than those of previous volumes are the 139 articles and the numerous others referred to by title only.

The Thyroid Gland. By CHARLES H. MAYO, M.D., and HENRY W. PLUMMER, M.D. Pp. 83. St. Louis: C. V. Mosby Company, 1926. Price, $175. A résumé of thyroid anatomy, physiology and bacteriology, broadly interpreted by a master of the subject.

PROGRESS

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W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Studies on the Biology of Streptococcus.—F. A. Stevens and A. R. Dochez (*J. Exper. Med.*, 1926, **43**, 379) write that certain characteristics are peculiar to groups of streptococci associated with certain diseases. Hemolytic streptococcus has been shown by numerous observers to have a direct relationship to scarlet fever and more recently Birkhaug has shown that the same statement applies to streptococci isolated from the margin of the inflammation in cases of erysipelas. The basis for these differentiations of the several groups of streptococci has been an agglutination reaction common to the strains isolated from a disease and for these strains to produce toxin which is neutralized by specific serum. The authors, in a series of a considerably large number of cases of erysipelas, show that the strains of human streptococci from cases of erysipelas agglutinate in a high per cent of instances with immune serum—in a higher percentage of instances than scarlatinal strains. The erysipelas strains make up a closely related group of streptococci, while the scarlatinal strains form an equally compact group. These are related antigenically, but the relationship is not so close as it is in the strains within the two groups.

Experimental Heart Disease.—George R. Herrmann (*Am. Heart J.*, 1926, **1**, 485) in an extremely careful study of experimental aortic insufficiency in animals shows that with this particular experimental procedure cardiac hypertrophy can be readily induced in young dogs and frequently in older animals and that this hypertrophy may appear

as early as the eighteenth day after operation and a maximum grade may be reached in about one hundred and ten days. In addition to the important contributory factor of youth, the presence of intracardial infection contributes to an important degree to the production of cardiac hypertrophy. It is of interest to note that in this study electrocardiograms failed to show the signs which suggest left ventricular preponderance. Another interesting observation is that the Austin Flint murmur occurred with great frequency, suggesting that this particular sign, with diastolic thrill, is dependent upon involvement of the posterior aortic cusp.

The Type of Phagocytic Cell and its Relative Proportions in Human Bone Marrow and Spleen, as Identified by the Supravital Technique, with Special Reference to Pernicious Anemia.—Last year Sabin, Doan and Cunningham demonstrated by vital staining that the mononuclear cells of the reticulo-endothelial system consist of two distinct strains—monocytes and clasmatocytes. The clasmatocyte was shown to be of great importance in the destruction of red blood cells that were not functionally efficient. In the present paper, CHARLES A. DOAN (*J. Exper. Med.*, 1926, **43**, 289) reports upon the study of the bone marrow in pernicious anemia and in other conditions. He finds that clasmatocytes are increased in number three or four fold in the bone marrow of individuals with pernicious anemia as contrasted with other diseases. In the spleen these interesting cells are markedly diminished. In addition to the large number of clasmatocytes that are found in the bone marrow, these cells show extra phagocytosis. Many of the cells contain more than 20 congested erythrocytes and a large number of these erythrocytes are nucleated red blood cells despite the fact that the peripheral blood shows only a very occasional normoblast. Doan infers from this study that abnormally stimulated clasmatocytes ingesting not only the old but also immature young red cells which had not been sent to the general circulation. The nature of the stimulus is not known, but this finding indicates an explanation of the interesting pathological anomaly of the hyperactively functioning red marrow in the face of a rapidly progressing anemia. The large phagocytic clasmatocytes destroy large numbers of red cells before they have an opportunity to function and this destruction of the cells in the bone marrow is sufficiently pronounced to occasion a severe anemia. The reduction of these cells in the spleen leads to the inference that this organ does not take any direct, active part in destroying red cells in pernicious anemia.

Nuclear Inclusions in the Testicles of Monkeys Injected with the Tissue of Human Varicella Lesions.—T. RIVERS (*J. Exper. Med.*, 1926, **43**, 275) writes that there has been evidence brought forth to show that there is a close relation between chicken pox and herpes, either simplex or zoster. These diseases are characterized by the appearance of fever, papules and vesicles, showing destruction of the skin and infiltration with polymorphonuclear and mononuclear cells. In addition to this, eosin-staining inclusions in the epidermal cells and the endothelial leukocytes are very characteristic. These inclusion bodies have been found in experimental herpes and in the lesions produced

by Virus III of rabbits. Just what these nuclear inclusion bodies are is not known. It is a question whether they are products of degeneration or whether they are the virus itself. Rivers states that he has never found them save in virus diseases. Fourteen experiments are detailed in this paper. Monkeys of different species were employed and the fluid from the vesicles and emulsified papules of the vesicles collected from patients with chicken pox was used for inoculation. In none of the animals was any lesion produced except in 4 African vervets, a species of monkey. Inoculations were made into the testicles of all the animals, but only in these 4 vervets were these inclusion bodies found. Their occurrence in these animals seems to offer very definite proof indeed that the disease, varicella, is a virus disease, the nature of which is unknown and the possibility of transmitting it to a series of animals is as yet undetermined.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Strangulated Hernia, from the Standpoint of the Viability of the Intestinal Contents.—Bellar and Colp (*Arch. Surg.*, 1926, **12**, 901) say that of 187 cases of strangulated bowel, resection was deemed necessary in 22 cases (11 per cent), with a mortality of 40 per cent. This is a high mortality but it must be remembered that 3 cases were frankly gangrenous and exceptionally poor operative risks. In 82 cases in which the omentum was strangulated, 30 or 36 per cent were resected with only 3 deaths. After the herniotomy a hernioplasty may be done provided the patient's condition permits. The postoperative complications were surprisingly small. There were 15 cases of respiratory infections, 7 wound infections, 12 hematomas, 1 femoral and 1 pulmonary embolism. Of the 36 deaths, 23 were accounted for by a combination of shock and intestinal obstruction, while 4 were by peritonitis, 2 by cardiac failure and 1 by bronchopneumonia. In other words about two-thirds of the mortality was from the effects of the intestinal obstruction. The total mortality for the reported series was about 12 per cent. In the inguinal hernias it was 10 per cent; in the femoral 14 per cent and in the umbilical 26 per cent. Early operation and local anesthesia are great factors in the diminution of operative mortality. Whether jejunostomy and more frequent resection might reduce the mortality in these cases that have been strangulated beyond twelve hours remains to be seen.

Diverticulitis of the Sigmoid.—KEEFE (*Boston Med. and Surg. J.*, 1926, **194**, 577) claims that diverticula have been found in all parts of the colon from the cecum to the rectum, although they occur with greatest frequency in the sigmoid. They may produce little or no discomfort and the patient may live to old age. Again they may cause serious illness with involvement of adjacent structures and even may terminate in death. Diverticula may be found at any point on the circumference of the large bowel, but the greater number are on the sides between the mesocolon and the longitudinal muscular bands. As they increase in size, they pass through lines of least resistance toward the mesentery or appendices epiploicæ. The symptoms of sequelæ of diverticulitis resemble those of appendicitis with local manifestations in the left iliac region. Roentgenological examination is of the utmost importance in the diagnosis of diverticula. Carcinomatous, tuberculous, luetic disease and pelvic inflammatory conditions in women should be distinguished from diverticulitis. Cystoscopy may sometimes, though not always, disclose a sigmoidovesical fistula. Conservative surgery is the keynote. Too much should not be attempted in the presence of infection. Colostomy alone in the diseased areas of the colon allows the inflammation to subside and may render subsequent resection of the sigmoid easier of accomplishment.

Congenital Dislocation of the Hip.—PUTTI (*Surg., Gynec. and Obst.*, 1926, **42**, 449) state that the deformity was far more common in females with an average of 8 girls to 1 boy in a large series. In 60 per cent of the cases the dislocations were single; in 39 per cent the deformity was bilateral. The author notes the curious geographical distribution of the disease. In Italy, he found the deformity frequent in the northern provinces, rare in the south and almost unknown in Sicily. Dislocations can be the result of a number of factors of which the mechanical one is without any doubt, the most frequent if not the only cause. The writer emphasizes that it is of the greatest importance to recognize the dislocation as early as possible, even before the child has begun to walk. Therefore, it is necessary to appreciate symptoms that are not generally known or to which no importance is given. If the dislocation is unilateral, the cutaneous creases of the thigh, so evident in the infant, are no longer symmetrical. On the dislocated side they are proximally displaced while the inguinal and gluteal pleats are deeper and longer than on the normal side. The outline of the dislocated hip is more prominent. The luxated limb has a tendency toward external rotation. Abduction is slightly diminished. Shortening, while nearly always minimal is appreciable to the experienced eye. If the dislocation is bilateral there is no difference in length in the limbs, but the pelvis appears enlarged because of the projection of the trochanters. Moreover the buttocks are flattened and the limb cannot be normally abducted. Ordinarily in the treatment of dislocation, the author uses the bloodless method, following the classical method of Paci. For the immobilization, he follows the methods of Lorenz. Immobilization periods are divided into two stages. In the first stage the limb is held in the classical first position of Lorenz for approximately three months; during the second stage that lasts from two to three months the limb is immobilized in a minor degree of right angle abduction and in internal

rotation. Great importance should be given to the physical treatment which must be undertaken when the period of immobilization ceases. Open intervention has not been altogether abandoned. It should be used only in those cases in which reduction cannot be obtained by the ordinary method. When reduction is attempted in patients of an advanced age and also in young patients, in whom the primary displacements are very marked and there is a misshapen capsule or serious anteversion of the femoral neck, failure may follow the Paci treatment. Then and only then must the surgeon play his last card by attempting the open operation.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

Respiratory Metabolism in Infancy and Childhood.—LEVINE, WILSON and RIVKIN (*Am. J. Dis. Child.*, 1926, **31**, 496) state that by use of the respiration chamber absolute and comparative measurements of the total carbohydrate oxidized by 5 children during short periods of fasting were made. There are certain limitations of the method but all in all it proves fairly satisfactory. Under similar conditions the total metabolism of all the children ranged between 12 and 20 per cent above their respective basal requirements and 2 normal girls, one obese but otherwise normal and the other subject to cyclic vomiting, oxidized approximately equal quantities of carbohydrate per square meter of body surface during equivalent fasting periods. They used from 144 to 155 gm. and from 192 to 201 gm. of carbohydrate per square meter in the intervals between eight and fifty hours and eight and twenty-four hours respectively. Under the same conditions, except for a reduced carbohydrate content in the storage diet and for the same duration of fasting, one boy suffering from a moderate form of diabetes mellitus, metabolized considerable small quantities, namely, 92 and 135 gm. per square meter respectively. The fact that the glycogen deposits are replenished during high carbohydrate feeding and that carbohydrate is mobilized for oxidization during starvation was shown by these tests. In this study the experimental conditions were not suitable for making quantitative measurements of the comparative efficiency of glycogen formation. The results clearly showed, however, that glycogen was adequately formed in the patient with cyclic vomiting. If these results were found to apply to other children suffering from the same condition they would imply that a diminished capacity for glycogen formation is not a factor in the hypersusceptibility of these children to ketosis. A defective mechanism of glycogen formation was a factor in producing the low tolerance for carbohydrate that was present in the boy with diabetes mellitus. Under maintenance conditions, the relative quantities of carbohydrate mobilized from fully replenished

stores and oxidized during short periods of fasting were approximately the same as in normal children, irrespective of their nutritional state. Between attacks and during resting conditions the quantity was not diminished in the patient with cyclic vomiting. As indicated from the data of one case, defective glycogenolysis does not apparently explain the exaggerated tendency of these children to ketosis.

Uric Acid and Creatinin in the Urine of Infants.—Rougichitch (*Am. J. Dis. Child.*, 1926, **31**, 504) measured the uric-acid excretion for twenty-four hours in a series of 22 male infants. The diet of the infants was purin-free and the amounts of uric acid found are regarded as of endogenous origin. In contrast with most of the hitherto published measurements of uric acid in the urine of infants, a closely constant daily excretion was found for the individual and a fairly constant value per unit of body weight was found for the group of infants, the range being from 14 to 25 mg. of uric acid per kilometer of body weight. Except in the case of an infant with active rickets whose uric acid excretion was high, 36 and 34 mg. per kilometer of body weight, no relationship of nutritional state to uric acid excretion was apparent. The uric acid excretion was also apparently independent of the age. It is suggested that the relatively high level of excretion of endogenous uric acid by infants may be explained by their high protein intake. It has been shown by Folin and others that a high intake of protein retards the destruction and accelerates the excretion of uric acid. The author admits that in this series the relationship of urine nitrogen to uric acid was not close. The uric-acid nitrogen ranges from 1.25 to 3.5 per cent of the total nitrogen. Measurements of urine creatinin in the same group of infants supported the conception of a close constancy of creatinin excretion in terms of the protoplasmic mass of the body. This range was from 10 to 15 mg. per kilometer of body weight. The highest values were observed in malnourished infants, probably because of their relatively larger mass of active tissue. There was no apparent relationship to creatinin excretion to differences in sleeping time or of muscular tonus. In the case of an infant having severe generalized convulsions, a creatinin excretion 3 to 4 times higher than normal was observed. Another baby with slight localized convulsions was found to excrete an approximately normal amount of creatinin.

Intradermal Salt-solution Test in Cardiac Diseases in Children.—Olmstead (*Arch. Int. Med.*, 1926, **37**, 281) tested 47 children with rheumatic heart diseases or allied conditions and he found that the disappearance time of intradermally injected salt solution is above fifty minutes in well-compensated nontoxic cardiac diseases, acute rheumatic fever and chorea. In cardiac decompensation with edema shortening of disappearance time was limited to edematous and preëdematous regions and was noted earliest in the dependent parts of the body. Decrease in disappearance time did not precede other clinical signs of impending decompensation with enough constancy to make the test of much value in predicting a break in compensation. In certain severely ill children having cardiac disease without decompensation, there was a marked and nearly equal decrease in disappearance time in the arm and leg. The intradermal salt-solution test was of value in this gen-

eralized or toxic group in rendering an unfavorable prognosis. The disappearance-time picture characteristic of the toxic group was altered in the direction of that characteristic of the decompensation group, if cardiac decompensation developed. In two patients tested after death the disappearance time in edematous parts was practically as short as during life which demonstrated that under these conditions circulation of the blood was not necessary in the phenomenon of the disappearance of intradermally injected salt solution.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY AT THE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,

AND

CLEVELAND J. WHITE,

UNIVERSITY OF BUFFALO, BUFFALO, N. Y.

Microchemical Studies of Arsenic in Arsenical Pigmentation and Keratoses.—Earl D. Osborne (*Arch. Dermat. and Syph.*, 1925, **12**, 773) demonstrated conclusively the presence of arsenic trisulphid in crystalline form in sections of skin from patients with arsenical keratoses and pigmentation; the microchemical studies being especially directed toward the relation of the arsenic to the tissue cells. Using essentially the same technique as Brünauer's modification of Justus' method, the section of keratosis showed the crystals to be between the cells (occasionally apparently intracellular), in the horny layer, and in the other layers, with particular localization in the basal. Arsenic was also present to a lesser degree in the stratum corneum of the normal skin surrounding the keratosis. The area of greatest arsenic deposit was in the basal layers of the epidermis, in the papillæ of the corium, especially under small-fissured areas of necrosis, and in the coil-gland duct cells near the epidermis. Hence the author concludes that the logical explanation for the development of epithelioma from arsenical keratoses is the deposition of arsenic in the papillary and subpapillary layers of the skin. As the action of arsenic in the body is one of oxidation and reduction, the activities of the cells are greatly increased and carried to a point of exhaustion and necrosis; hence the cells of the epidermis may very easily undergo malignant changes because of this stimulation. In sections from the skin of a man having typical arsenical pigmentation, the crystals were found in large amounts in the entire epidermis with no relation to the amount of pigmentation. It was distributed evenly extracellularly; a few crystals appeared to be within the cells. The upper parts of the corium contained large amounts of arsenic, especially in the papillæ; the sebaceous glands and ducts contained a great deal; the sweat glands and ducts, a very small amount. The author feels that the arsenic produces the pigment by indirectly acting on the mother melanin substance in the corium to form the finished product. These studies indicate that the pigment itself does not contain the arsenic.

Physical Allergy as a Cause of Dermatoses.—W. W. DUKE (*Arch. Dermat. and Syph.*, 1926, **13**, 176) suggests the name physical allergy for altered reaction caused specifically by the action of physical agents such as light, heat, cold and mechanical irritation, and in the case of heat sensitiveness, indirectly by the effect of mental or physical exertion. The reactions produced are of two varieties: (1) Contact reactions in which the reaction is confined to the point of contact between a surface and the irritating agent; (2) reflex-like reactions which occur not only at the site of contact but in distant structures as well. General symptoms follow contact if the surface exposed is large enough. In both contact and reflex-like reactions there are three types of skin eruptions, namely, the immediate reactions, consisting of erythema, pruritus, and edema, that is, urticaria; delayed reactions in which the urticarial reaction is slight and is followed by dermatitis, and, finally, solitary reactions which consist of wheals or other skin anomalies covering limited areas and appearing under the influence of extremely small amounts of heat or cold, as the case may be. Sensitiveness to heat is more common than sensitiveness to cold; frequently, patients sensitive to heat react only after previous exposure to cold and *vice versa*, and patients sensitive to cold react to cold only after previous exposure to heat. In cases of delayed reaction to various agents the diagnosis is extremely difficult and uncertain and can often be made only by comparing the symptoms with those of patients who react promptly. Two possible theories are suggested for skin reactions resulting from physical allergy, namely, (1) patients, coming as they do from allergic families, may become specifically hypersensitive to some new body formed in their tissues solely under the influence of one specific physical agent and react to this body just as persons sensitive to pollen react on contact with pollen; (2) then, it may be presumed that in the body we have chemical substances which are capable of being transformed under the specific influence of certain physical agents to give rise to the nerve impulse which is recognized by the brain as having been caused by that agent. As to the mechanism involved, one might assume that the action of the physical agents in the contact cases was directly upon the peripheral tissues or peripheral efferent nerve endings, while in the reflex-like cases the action was exerted on sensory or afferent nerve terminals. Avoidance, of course, is not always possible; then treatment with the agent which causes reaction, with a view to increasing tolerance, should be tried. Any agent which improves the general health is likely to reduce the severity of the symptoms, especially those sensitive to heat who, on relief of any debilitating influence, either mental or physical, are likely to become more tolerant.

The Salicin Treatment of Psoriasis.—GEORGE PERNET (*Arch. Dermat. and Syph.*, 1926, **13**, 111) maintains that the use of salicin by mouth will often check and clear up acute and subacute attacks of psoriasis. It must be prescribed in a solution made up from the crystals, the dose being gradually increased from 1 to 2 gm. in 30 cc. of water immediately after meals. Salicin is of no value if taken in the form of tablets. In reviewing a number of cases, all with relief, it was found that one had had no return for eleven years. The author does not consider salicin as a prophylactic and discourages its use after its effects have been obtained in an acute or subacute attack.

OBSTETRICS

UNDER THE CHARGE OF

NORRIS W. VAUX, M.D.,

CLINICAL PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA,

AND

CLIFFORD B. LULL, M.D.,

CLINICAL ASSISTANT IN THE OBSTETRICAL DEPARTMENT, JEFFERSON MEDICAL COLLEGE PHILADELPHIA.

Inversion of the Uterus.—PHANEUF (*Am. J. Obst. and Gynec.*, 1926, **11**, 171), confines his discussion to the puerperal inversions, and these are classified as incomplete and complete, the latter being when any part of the corpus uteri passes through the cervical ring. Acute cases are those which have lasted a month or less; the chronic, those which have been inverted beyond that period of time. It is shown that this obstetric complication occurs once in 125,000 labors as an average. With constant improvement of obstetric practice, this frequency is becoming less. As the etiologic factors playing the most important part in the production of inversion of the uterus three are mentioned as the usual factors in the production of this lesion: (1) Undue relaxation of the uterine wall; (2) pressure from above; (3) traction on the umbilical cord. As contributing factors, Credé method of placental expression on a relaxed uterine musculature and fundal placental attachment before placental separation, a short cord, coughing or sneezing. The diagnosis is made by vaginal examination with a speculum, where can be seen a soft pear-shaped tumor filling the vagina of red or gray color. On abdominal examination no fundus uteri is felt, but a cup-shaped depression is distinctly felt in its place. The mortality is gradually improving, and now stands at about 34 per cent in acute cases and in the chronic type 6 per cent. The treatment is nonoperative except in chronic cases. The mass or inversion is replaced by pressure upward or manual reposition followed by uterine gauze pack. The Spinelli operation seems the one of choice in chronic cases. All cases show systemic shock with moderate or severe hemorrhage.

Syphilis in Pregnancy.—FROST (*California and West. Med.*, 1926, **24**, 63) states that a pregnant woman may have syphilis of any type and in any stage. Usually it is the latent type and the complement-fixation test may or may not be positive. The Sachs-Georgi reaction, a recently introduced precipitation test, seems the most reliable modification of the Wassermann test in these cases. The syphilitic virus acts in the production of abortion or stillbirth in pregnant women. During antisyphilitic treatment the Herxheimer reaction may be responsible for abortions; this can be obviated and a series of mercurial injections or rubs before arsphenamin is given. Early and thorough treatment carried through the entire pregnancy to two weeks before term gives practical assurance of a healthy child being born.

A New Technique of Unmodified Blood Transfusion.—Brooks (*California and West. Med.*, 1926, **24**, 44) stresses the need of using properly cross-typed uncitrated blood to avoid untoward reactions in blood transfusion. He uses glass paraffin-coated tubes with special needles, each cylinder having a capacity of 300 cc. and having a glass airway on the side to which a pressure suction bulb is attached. The cylinder is sealed and the blood drawn from the donor by suction, a positive pressure being used to inject the blood into the recipient. The collection of blood requires one minute and the injections take one or two minutes; blood is thus transferred while still warm and before any coagulation changes have taken place. He has used this method in 216 cases with no undesirable reaction following its use.

Appendicitis in Pregnancy.—Royston and Fisher (*Am. J. Obst. and Gynec.*, 1926, **11**, 184) state that although appendicitis in pregnancy is a dangerous complication of pregnancy, it appears to be relatively uncommon, the relative frequency being about 1 per cent. The mortality of the suppuration cases is high, 30 per cent in the operative cases and 80 per cent in the nonoperative cases. In about 40 per cent of the cases abortion, miscarriages or fetal death occurred. The progress of this complication of pregnancy is most striking in that the cases usually progress rapidly with little tendency to localization and abscess formation. The diagnosis is not difficult—local pain and tenderness and rigidity over appendix region—while fever, leukocytosis, nausea and vomiting are frequently absent in the early cases, coming on after the infection has begun to spread. The early diagnosis, excluding the urinary-tract infection, gaseous distention of the intestines, pelvic conditions, as tender adenexia and the remote probability of gall-bladder and duct diseases, must always be seriously considered. The author sounds warning that too much valuable time should not be consumed in laborious differential diagnosis; if the appendix is suspected operate, as the results obtained in early months of pregnancy are as good as those in the nonpregnant women and the danger of abortion very slight.

The Danger of Malformation of Fetus in Roentgen Ray Treatment during Pregnancy.—Emil Ries (*Am. J. Obst. and Gynec.*, 1926, **11**, 361 presents a case of markedly deformed fetus born dead at term to a woman who had had Roentgen ray treatment for uterine hemorrhage one hundred and fifty-nine days before the birth of the fetus. He raises the question of the connection between the Roentgen ray and the malformation of the fetus.

Full-term Extrauterine Pregnancy, with Report of Three Cases.—Lucien A. LeDoux (*Am. J. Obst. and Gynec.*, 1926, **11**, 395). Three cases are reported in detail, 2 cases were followed by maternal death when the fetus was found viable at operation, 1 case of dead fetus had a favorable maternal outcome. In the period from 1906 to 1925 the author found 367 cases of extrauterine pregnancy of which number, 11 were full term. He concludes that laparotomy is the only safe method of delivery. The prognosis is more favorable to the mother in cases in which the fetus is dead because of the obliteration of the placental circulation.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Treatment of Uterine Fibroids.—An interesting statistical study of a large series of fibroids which were treated in the gynecological department of the Mercy Hospital in Pittsburgh has been presented by WEISS (*Am. J. Obst. and Gynec.*, 1926, **11**, 343). He has divided the series into two groups representing five-year periods and has found that there were ten deaths or a mortality of 2.7 per cent, among those operated upon during the first five-year period. The percentage of deaths in this group is higher than in the second five-year series, when radium was largely used, and he believes that the first-period mortality would have been much less had the treatment been nonoperative. In the second five-year group the mortality in 747 fibroid cases treated by operation or irradiation was ten deaths, or 1.6 per cent, but in the operative group the mortality was 2.3 per cent. Only one death followed radium treatment, occurring in a patient who had myocarditis and nephritis of such a pronounced type that in all probability the radium treatment was not a factor in causing death. In this second five-year period, it is shown that the ratio of myomectomies to hysterectomies is practically the same as in the first group, namely, about 1 to 5. In this second group 197, or 26 per cent of all cases were treated with radium, and 21, or 2.8 per cent were treated by myomectomy and radium. Although a certain percentage of fibroid uteri treated with radium have later become pregnant, yet he is of the opinion that unless definitely contraindicated, myomectomy is preferable in a women who desires to bear children. This is particularly true in tumors of the interstitial or subperitoneal variety. Unless radium is used in sufficiently large dosage to cause a shrinkage of the tumor with the incidental bloodvessel contraction and atrophy of the ovaries, no definite result is obtained, and when it is used to produce these results, the childbearing function is lost. The patient should be told very definitely that radium as generally employed deprives her of future pregnancy and may likewise produce menopause. It is admitted that smaller doses of radium frequently produce excellent conservative results but in view of the fact that there is no known method of estimating the radium resistance or susceptibility in different individuals, we must be most careful in our prognosis.

Tissue Reactions to Radiation.—Owing to the immense importance of correct methods in radiation therapy, it has seemed worth while to EWING (*Am. J. Roentgenol.*, 1926, **15**, 93) to review the present state of

our knowledge and to summarize the great mass of observations that has accumulated during the past decade, especially with relation to tissue reactions. Ewing is recognized as one of the foremost pathologists in this country and he has given close attention to the effects of radiation on the tissues, and, therefore, it is indeed fortunate that we can avail ourselves of his carefully worded summary. From his own observations as well as from a digest of the literature he is of the opinion that the cure of carcinoma by radiation results from a nice adjustment between injury to tumor cells, assuring their partial or complete necrosis, and injury to surrounding tissues, eliciting a reactive reparative inflammation which removes tumor debris and often destroys viable tumor cells. These tissue reactions are specific in the sense that, taken as a whole, they are not observed under any other conditions. Effective radiation occurs only in tumor tissues which are in an approximately normal state of growth and nutrition and upon tissues which are vascular, well nourished and capable of inflammatory reaction. Dividing cells and rapidly growing tumors are more susceptible than resting cells and stable tumors, but this difference is not invariable. The three main methods of irradiation, the single, the fractional, and the prolonged dosage, each produces different tissue reactions, and it is desirable that the choice of methods should be determined, as far as possible, by the character of the reaction it is desired to produce, and not merely by the therapeutic effect generally obtained. A high total dosage is the first essential in destroying most true carcinomatous processes, and as a rule the most tumor destruction and tissue reaction, and the best results, are obtained by delivering this dosage as soon as possible. Radium probably tends to produce more specific selective effect on tumor cells, and Roentgen rays more injury and reaction of the connective tissue. A large part of the destructive effect of rays upon tumors, especially the necrosis of single cells or large masses, in bulky or encapsulated tumors, is caused by interference with the blood and lymph circulation. Extended observations of the histological changes produced by different doses on the different tumors must be accumulated before radiation therapy can be taken out of the field of therapeutic empiricism and rendered safe, effective, and uniform. Increased interest and importance thus attaches to the careful and thorough histological study of tumors before and after irradiation. Effective irradiation excites a favorable reaction on the part of the body as a whole. The nature of this reaction is complex and the factors largely unknown. It is probably of much importance in the cure of malignant tumors by radiation.

Muscle Transplantation in the Treatment of Urinary Incontinence.—Many operations have been devised to relieve urinary incontinence which is the result of damage to the sphincter muscle of the bladder, and some of these operations occasionally give brilliant results although frequently they fail of their purpose. When, however, there is no sphincter muscle present which can be repaired, the problem becomes, indeed, a difficult one. In a case reported by DEMING (*J. Am. Med. Assn.*, 1926, **86**, 822) the condition which caused urinary incontinence was a congenital epispadias in which there was neither an internal nor an external sphincter muscle present. After several of the usual opera-

tions had been performed, the idea of transplanting the gracilis muscle from the thigh to the urethra to make a new sphincter muscle was considered and the operation performed with a rather satisfactory result. The operation for transplanting the gracilis muscle is not a difficult one. The incision is carried from the pubic spine downward over the middle of the thigh, which, if abducted, will readily disclose the course of the muscle in the most prominent portion of the operative field. The deep fascia of the thigh is opened, and the muscle in question traced downward well toward the knee. The muscle has a double nerve supply and can easily be freed together with its vessels. It is desirable to get as long a muscle belly as possible and incise it between the two areas of nerve supply. The proximal portion can readily be wrapped around the urethra in which a catheter has been inserted, sutured back onto itself and fastened to the under surface of the pubic arch. Fine double-zero chromic sutures were used. The subcutaneous layer was closed with zero plain catgut and the skin with interrupted black silk. The wound was painted twice a day with 1 per cent mercurochrome-220 soluble and the bladder was irrigated daily with potassium permanganate solution, 1 to 10,000. The wound healed by first intention, and the patient discharged the third week. There are several advantages in using the gracilis muscle. In the first place, the loss of its normal function does not in any way impair the locomotion of the patient. It is easily accessible, lends itself readily for transplantation, and has a double nerve supply. The nerves and vessels to the upper portion of the muscle lie so high up that a long belly of muscle can be turned upward without interference with these structures. Its transplantation is recommended for those cases of incontinence due to the congenital absence of bladder sphincters and in those cases in which the sphincters have been destroyed.

OPHTHALMOLOGY

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.,

HEAD OF THE SCHOOL OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.

Preventive Treatment of Cataract.—Borsch (*Rev. gen. d'opht.*, 1925, **39**, 246) believes that opacities of the crystalline lens are frequently due to ocular toxemia from the absorption of toxins from the stomato-gastrointestinal tract, and carried by the bloodvessels or lymphatics to the different organs, as also to the eye, where they cause diminution of the resistance of the tissues and favor the formation of opacities. Errors of refraction, by the ocular fatigue which they induce, also cause slight but continuous congestion, which likewise predisposes to the development of opacities. Such errors of refraction must not only be carefully corrected but glasses with the property of filtering the irritant

rays should be prescribed. He recommends treatment looking to gastrointestinal, dental and tonsillar disinfection, and local treatment by ocular douching with astringent, stimulating and antiseptic solution to favor the coagulation of the blood and lymph and the expulsion of toxins. He has found that such treatment frequently causes incipient opacities to disappear, retards presbyopia and prolongs the period of useful vision.

Radium in Ocular Therapy.—DeGentile (*Clin. Ophth.*, 1925, **14**, 18) gives the indications for radium treatment of various diseases of the eye; injuries to the organ can be avoided by proper precautions; in the usual method of application slight inflammation of the skin or conjunctiva may occasionally occur, but damage to the retina or optic nerve never. Radium is to be recommended in cicatricial keloid of the lids, as in lupus of the skin and conjunctiva; healing takes place without much shrinking. The same treatment is superior to all other methods in vernal conjunctivitis. In inflammatory disease of the cornea radiation does not exert the same favorable influence in all forms; it is particularly inferior to the usual methods in acute inflammatory affections; it is the method of choice in angioma of the lids. Lymphoma of the lids does equally well under radium as under the Roentgen rays. Carcinoma of the lids, which has not yet extended to the tarsus or adjacent bones is completely cured by radium without disfiguring cicatrices. In glioma of the retina the results of radium treatment are bad. In malignant disease of the orbit, radium treatment following surgical operations may prevent relapses. Radiation of the hypophysis gives similar results to that of the Roentgen rays. The symptoms of exophthalmic goiter, including the exophthalmos, are favorably influenced by radiation of the thyroid.

The Result of Treatment by Artificial Light on Phlyctenular and Other Tuberculous Lesions of the Eye.—Nutt (*Brit. J. Ophth.*, 1926, **10**, 138) selected a series of cases of phlyctenular disease of the eyes and in addition to use of tuberculin-cod-liver-oil emulsion with hypophosphites and local treatment, subjected them to irradiation from a mercury vapor arc. The patients strip and are exposed to the rays back and front; there is a nurse in charge who times the exposures, which commencing with ten minutes a day for the first few days, are gradually increased to one hour per day. The eyes are protected by wearing London smoked glasses. The cases treated fall under two headings: (1) the chronic cases that had been under treatment for a long period previously, with little if any improvement; (2) the recent cases treated as soon as they appeared in the outpatient department. The first group comprises cases with histories extending from five months to four years before treatment with the ultraviolet rays was commenced. There was exhibited in this first group a case of sclerosing keratitis; 1 of pannus; 2 of persistent marginal ulceration; and a strumous keratitis. Very good results were obtained in from four to fifteen weeks in all cases. The second group of recent cases responded equally well but are still under observation. Many of the cases give a violent reaction to tuberculin.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

DEWAYNE G. RICHEY, B.S., M.D.,

MERCY HOSPITAL, PITTSBURGH, PA.

Bacteriologic Studies of the Respiratory Passages: VI. Hemolytic Streptococci in the Pharynx and Tonsils of Infants and Children.—"The importance of hemolytic streptococci as the cause of fatal infections in infants and children is generally recognized." Having previously shown that these streptococci are commonly found in normal and diseased conditions of the upper respiratory tract, occurring in 61 per cent of swab cultures from the pharyngeal and tonsillar surfaces, and in 97 per cent of cultures from the tonsillar crypts, and in 61 per cent of extirpated adenoids of children, aged from six to fifteen years, PILOT and TUMPEER (*Am. J. Dis. Child.*, 1926, **31**, 22) undertook to determine the incidence of hemolytic streptococci in children under six years of age. All of the 28 children were afebrile and presented hypertrophic tonsils and adenoids. Cultures were taken from the bottoms of the crypts of the extirpated tonsils and cultured aërobically in meat infusion blood agar. Hemolytic streptococci were encountered in 25 or 28 (89.3 per cent) in one or both tonsils. As in previous studies, it was noted that on the surface of the tonsils the organisms were fewer than in the crypts. Cultures from the removed adenoid vegetations of 11 children of the same age range showed hemolytic streptococci in 6 (55.5 per cent). A further study was made of the incidence of hemolytic streptococci in the throats of normal children, aged from six weeks to ten years. Swab cultures were secured separately from the pharynx and each tonsil, and were inoculated into melted blood agar. Thirty-six of 75 persons (47.7 per cent) gave positive cultures from one or both tonsillar surfaces and 19 (25.3 per cent) from the pharynx. Two infants, aged six weeks, both gave positive cultures. In practically all instances the number of hemolytic streptococcus colonies constituted less than 10 per cent of the total number of colonies. According to Holman's classification, all but two strains corresponded to Streptococcus pyogenes. Five strains, selected at random, were injected intravenously into young rabbits, all of which developed purulent arthritis within four days, and in one a marked thrombo-ulcerative, mitral and aortic endocarditis with multiple infarcts of the spleen and kidneys was encountered. The authors conclude from their researches that in young infants and children, as in adults, hemolytic streptococci reside normally in the tonsil and adenoids; and that "from these sources the streptococcal complications in the course of other diseases commonly arise."

Diphtheria following Tonsillectomy. Local Resistance and General Immunity to Diphtheria.—The serious nature of diphtheria as a complication following tonsillectomy is due to the fact that the disease is likely to be overlooked until it is almost too late for antitoxin adminis-

tration. The postoperative sloughing membrane following the removal of the tonsils closely resembles a diphtheritic pseudomembrane, and is, therefore, a source of great danger in overlooking the superimposed secondary diphtheria. In reporting 4 cases of diphtheria which occurred in the fauces immediately after tonsillectomy, ZINGHER (*Am. J. Dis. Child.*, 1926, **31**, 72) emphasized the danger of this condition to indicate the necessity of taking nose and throat cultures before operations on these structures, and to protect positive diphtheria carriers by a prophylactic dose of antitoxin—in children, of course, who did not have a negative Schick test. Of the 4 children, whose clinical records are given in the context of the article, 1 died and the other 3 were saved at the eleventh hour by recognition of the disease, although all of them developed a diphtheritic paralysis of the palate, and in 1 patient convalescence was complicated by an attack of aspiration pneumonia. In commenting upon his subject the author recognizes that while these three factors—absence of general immunity to diphtheria, presence of virulent diphtheria bacilli in the nose and throat, and an operation such as tonsillectomy—may not come together frequently, yet when they are present in the same person, diphtheria is quite certain to follow and the disease is likely to prove very dangerous, possibly fatal. The serious nature of the superimposed diphtheria arises from the danger of an early and rapid absorption of a fatal dose of toxin from the extensive raw surface, and the difficulty of recognizing the disease in the sloughing postoperative membrane until much valuable time has been lost and the opportunity for effective administration of antitoxin has slipped by. Diphtheria may also readily develop as a result of a superimposed infection with diphtheria bacilli occurring in a susceptible person from one to two weeks after an operation on the tonsils and adenoids. At this time the wound has not yet completely healed, and the resistance of the mucous membrane to infection is still below normal. Such conditions show how necessary it is that patients who are to be operated on for nose and throat conditions should be constitutionally immune to diphtheria, irrespective of whether the throat cultures taken before the operation are positive or negative for the Klebs-Löffler bacillus. To accomplish this general immunization of all young children with toxin-antitoxin or with toxoid would be a very desirable procedure. If the nose and throat cultures are positive for diphtheria bacilli, the author advises a prophylactic dose of 1500 units of diphtheria antitoxin, before such operations, unless the patient has already been tested with the Schick test and shows a definite negative or a negative pseudoreaction.

The Therapeutic and Prophylactic Value of Tonsillectomy in the Active Stage of Vincent's Angina.—WESTLAKE (*Ann. Otol., Rhinol., and Laryngol.*, 1925, **34**, 1121) after a review of the literature, found nothing that indicated a way of successfully and surely terminating repeated attacks of Vincent's angina on the tonsil. He reports the clinical and bacteriologic data of 15 cases whose tonsils were removed during the active stage of the disease. From his observations the author concludes that an active, severe Vincent's angina is no contraindication to tonsillectomy; that relief from symptoms followed the operation; that no recurrences have been observed; that the tonsil must be an

important factor in the chronicity and recurrence of the disease; and that the spirilla and fusiform bacilli associated with the disease almost instantly disappear after the tonsillectomy—a fact for which no satisfactory explanation has been found.

RADIOLOGY

UNDER THE CHARGE OF

RUSSELL D. CARMAN, M.D.,

HEAD OF THE SECTION OF ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.,

AND

CHARLES G. SUTHERLAND, M.B.,

ASSOCIATE IN SECTION OF ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

Dynamic Studies on the Cerebrospinal Fluid in the Differential Diagnosis of Lateral Sinus Thrombosis.—"Increased intracranial pressure is normally propagated throughout the cerebrospinal fluid system and may be measured by a manometer employed in connection with lumbar puncture. Compression of the internal jugular veins causes increased intracranial pressure with immediate rise in spinal fluid pressure. It is now generally considered that absence of rise in fluid pressure on jugular compression (positive Queckenstedt sign) indicates spinal subarachnoid block, a most important and early sign in spinal cord tumor. It may be safely said that the criteria on which these tests depend and the results of the tests have been for the most part dependable. So much so, in fact, that the effect of jugular compression on spinal fluid pressure now forms one of the routine tests in diagnostic lumbar puncture." Recognizing that the mechanism is different, TOBEY and AYER (*Arch. Otol.*, 1925, **2**, 50) utilized this test in the diagnosis of lateral sinus thrombosis, where the absence of rise in pressure in the spinal fluid manometer is not due to obstruction of the fluid but to venous obliteration. With the patient in the lateral position, lumbar puncture is performed and the fluid is permitted to run into a glass manometer of 2-mm. bore. After the initial pressure reading, digital compression of one, and then the other, internal jugular vein is made, noting the rapidity of rise of the fluid column in the manometer. Then, for comparison, both sides of the neck are compressed simultaneously. In a typical case of lateral sinus thrombosis there is a prompt and rapid rise in fluid pressure to twice or three times the initial reading when the internal jugular vein draining the normal sinus is compressed. This pressure rise is maximal, being equivalent to the pressure attained when both jugular veins are compressed. Pressure over the vein draining the thrombosed lateral sinus causes either no rise or, more commonly, a slow rise of only from 10 to 20 mm. in the manometer. After having performed over 3000 punctures in cases in the neurologic clinic, the authors caution as to such

pitfalls of technic as abnormally low tension of the spinal fluid, persons with thick necks, abnormal rise in fluid pressure due to carelessness, normal difference on the two sides and anatomical variation in the size of the lateral sinuses. They also recognize two known dangers: (1) Sudden death from the presence of subtentorial abscess or tumor following lumbar puncture, and (2) the precipitation of acute meningitis, although in 20 cases of lateral sinus thrombosis they have not encountered any evidence of ill effect from the technic.

Stasis in the Ascending Colon Simulating Appendicitis.—CUNNINGHAM (*Radiology*, 1925, **5**, 480) has studied a series of cases in which appendectomy failed to relieve the symptoms. These patients are likely to have a hyperacidity or anacidity and a palpably filled cecum, often more tender after operation than before. With surprising unanimity roentgenologic examination has shown a delay of twenty-four hours or more in the cecum and ascending colon. The patients have done well on a diet tending to relieve stasis. Encouraged by these results, a group of patients who had not been operated upon were placed on similar dietary measures with gratifying effect. Treatment consists in giving two glasses of hot water before breakfast and at least six glasses of liquid during the day. Plenty of vegetables, bran or agar agar and whole wheat bread are advisable. If necessary, a level teaspoonful of sodium bicarbonate in water may be taken on arising to assure a thorough evacuation. Massage and exercise assist. Cathartics should be avoided, but, if required, a small amount of magnesia and liquid petrolatum at bedtime is the least harmful.

Roentgen Ray Examination of the Joints of Hemophilics.—DOUB and DAVIDSON (*Radiology*, 1926, **6**, 217) present 7 cases of hemophilic arthritis in which are found both early and late Roentgen ray changes. In the former of which there were two cases there was no bone destruction, the diagnoses being verified by aspiration of the joint. The late cases showed three definite distinguishing characteristics: (1) Cartilaginous destruction; (2) punched out areas of bone destruction, and (3) organized blood clot in the synovial cavity.

Some Effects of Mercury-vapor Arc Baths upon the Blood.—BANNERMAN (*Brit. J. Rad.*, 1926, **31**, 71) reports some observations on children following rather heavy single doses from the mercury-vapor lamp. In all cases there was a fall in the number of red corpuscles, occurring immediately and persisting for several days, to be succeeded in some cases by a rise above the original level. The total number of leukocytes may or may not be increased, but polymorphonuclear count is always increased. In many cases the mononuclear cells are reduced. Eosinophiles are markedly diminished, both relatively and absolutely, immediately after, and then gradually rise up to or beyond the original number. Sedimentation of cells in citrated blood increases after exposure, remains high for several days and is then reduced to or below the original level.

Complete Bilateral Duplication of Ureters and Renal Pelves.—McKINNERY and CARY (*Am. J. Roentgenol. and Rad. Ther.*, 1926, **15**, 149) present a case and briefly discuss the literature on this subject.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

ASSOCIATE PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Experiments on the Glomerular Distribution of Blood in the Mammalian Kidney.—Following the work of Khanolkar, in 1922, on rabbits, and Richards and Smith, in 1924–1925, on frogs, who were agreed as to the "partial activity" of the kidney, HAYMAN and STARR (*J. Exper. Med.*, 1925, **42**, 641) conducted a series of experiments on rabbits. They injected Janus-green B into the aorta, and counted the number of glomeruli which were thus intravitally stained. Nelson's method of estimating the number of glomeruli in a kidney was also used to count the number open at the moment of injection of the dye. Under their experimental conditions they found 42 to 100 per cent of the glomeruli were open in 13 control experiments. In 10 of these the figures fell between 56 to 89 per cent. Three experiments were made in which renal vasodilation was produced by caffeine and NaCl. They found nearly all the glomeruli were open during the action of these substances, showing that vasodilation is accompanied by an increase in the number of patent glomeruli. Vasoconstriction was successfully produced by means of adrenalin (9 cases) and CO_2 inhalations (2 cases), and in these the number of open glomeruli was usually reduced markedly in a few cases below 10 per cent. Their experiments to determine the relation of renal bloodflow to the number of open glomeruli, however, are too few in number to admit of much generalization. As a rule, they found the number of open glomeruli, the kidney volume, the renal bloodflow and the urine diminution all varied in the same direction. Experimental error in such experiments, however, is high, and there were exceptions to such a generalization.

The Soluble Specific Substance of the Friedländer Bacillus and the Pneumococcus.—In 1921 Toenniesson, working on the capsular material of a strain of Friedländer's bacillus reported the isolation of a snow-white, nonreducing, substantially nitrogen-free polysaccharide which gave a red color with iodine. After hydrolysis the reducing sugars gave an osazone. More recently the "soluble specific substance" of the pneumococcus, first observed by Dochez and Avery, has been identified with the polysaccharide portion of the organism. Now HEIDELBERGER, GOEBEL and AVERY (*J. Exper. Med.*, 1925, **42**, 701), in a series of three articles, publish the results of further investigations into this subject. They first make use of a strain of Friedländer's bacillus recovered from a spontaneous guinea-pig infection, and give their methods for isolation and purification of the soluble specific

substances. After enumerating its properties, they compare the chemical and immunological relationships of pneumococcus Type II and this strain of Friedländer's bacillus. They show marked similarity in certain immunologic reactions, but do not show reciprocal absorption of agglutinins and precipitins. This may be partly due to impurities. The writers themselves think the serologic and antigenic similarity of these biologically unrelated organisms is an example of heterogenic specificity among bacteria. In their third article some refinements in the methods of isolation of the soluble specific substances of Types II and III pneumococcus are described which have yielded a nitrogen-free form with much enhanced activity with immune serum. A soluble specific substance from Type I pneumococcus is also described which proves to differ from the substance obtained from the other two types. It would also seem so far that the polysaccharids isolated are the actual specific substances of the pneumococcus.

An Investigation of the Acid Fastness of Tubercle Bacilli.—In regard to the claims that a saprophytic strain of tubercle bacilli with greater powers of growth, less virulence and nonacid fastness, can be obtained by rapid and repeated culturing. SUYENAGA (*Am. Rev. Tuberc.*, 1925, **12**, 260) carried on a large number and rigorously standardized experiments. In an effort to produce such a strain he transferred every two days, and in different series used varying reactions from 1.5 per cent acidity to 1 and 2 per cent alkalinity, and again nonnutrient and ameba media. On the latter two media it was found that a marked reduction in acid fastness was present for several late generations and increased again, but that reaction variations had no precise influence on the staining qualities. The Gram positive character of the bacillus tuberculosis persisted after fragmentation, the acid fastness did not. Young cultures of old strains could take an aqueous methylene-blue color. The author feels that Marmorek's and other worker's claim of establishing saprophytic nonacid-fast strains is due either to other laboratory acid-fast contaminants or to varying ages of the cultures used for stain ing tests. This work only proves a variation in the degree of acid fastness which can be produced by rapid transfer on nonnutrient and ameba media.

The Attenuation of Tubercle Bacilli in Incubated Tuberculous Tissues.—A review of previous work done along this line is given by the authors WEBB, RYDER and GILBERT (*Am. Rev. Tuberc.*, 1925, **12**, 242) which in brief shows that subcutaneous plants of tuberculous lymph glands give the characteristic disease such as produced by virulent cultures but more chronic in type. It was found that incubation of the tuberculous tissue in sterile saline attenuated the virus almost up to the vanishing point by the tenth day. In progressing with this line of research the workers found that guinea pigs subjected to plants incubated ten days, and subsequently inoculated with virulent cultures ran a longer course of illness than the controls without the tuberculous tissue implants. Also emulsions of tubercle bacilli from chronic cases produced death much more slowly than those from acute. The increase in resistance produced by the incubated glands seem to suggest a means of getting protection, but the authors warn against any method which introduces live bacilli into a susceptible animal.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

Gastric Ulcer and Gastric Carcinoma; an Inquiry into their Relationship.—DIBLE (*Brit. J. Surg.*, 1925, **41**, 188) made a study of the relationship of gastric ulcer to gastric carcinoma on 170 specimens removed at operation. In a series of 126 ulcers in which the clinical and naked-eye evidence indicated that the lesion was a simple ulcer, microscopic examination confirmed this diagnosis; none of this considerable series of ulcers showed any malignant change. This finding is at variance with the opinion of many authorities. Of 33 cases of carcinoma examined, 19 showed no evidence suggesting a preëxisting carcinoma. In 9 the weight of evidence was against any association with chronic ulcer. In the remaining 5 cases the supervention of malignant disease on chronic ulcer was suspected on the basis of histologic evidence alone. A history likely to be given in a case of ulcer which has become cancerous was given in 2 of these 5 cases. It may therefore be concluded that in only 2 of 33 cases of gastric cancer did the entire weight of evidence, clinical and histologic point to a direct connection between the two conditions. Balfour of the Mayo Clinic, on the other hand, concludes that the most important single factor influencing the life expectancy of a person operated upon for gastric ulcer is gastric cancer.

Calcium and Tuberculosis.—ISZARD (*J. Ind. Hyg.*, 1925, **7**, 505) declares that of 3,927,978 individuals employed in the United States in gainful occupations with exposure to industrial dusts, 152,417, or 3.8 per cent are exposed to dusts of a comparatively high calcium content. Authorities have placed dusts rich in calcium among the least harmful of the inorganic mineral dusts. The statistical data of the United States show that tuberculosis mortality is higher for all calcium dust industries than for the population as a whole. The percentage, however, is markedly lower than for those industries involving exposure to dust of high silica content. Furthermore, exposure to calcium dust appears to retard the development of the tuberculous process since in the calcium industries the tuberculosis mortality peaks are reached much later in the age scale than in other dusty trades. Foreign statistical data give one the impression that the calcium industries are beneficial especially the lime and chalk industries. Clinical and industrial reports point to either a harmless or a beneficial action of the calcium dusts. Animal experiments point rather to the fact that calcium dusts act as mild irritants, and, though playing no important role in the devel-

opment of tuberculosis, do not arrest its development. In the present experiment it was proposed (1) to test the effect of simple calcium dust, namely, hydrate of lime, on the lungs of experimental animals (2) to determine if it exerts any beneficial or detrimental action when there is a tuberculous involvement of the lungs. Rabbits were used and divided into the following group: Normal controls, tuberculosis controls, lime-dusted controls, lime-dusted animals with superimposed tuberculosis, and animals inoculated with tuberculosis with superimposed lime dust. It was finally concluded that calcium hydrate dust is not harmful to the lungs of rabbits. It apparently acts as a mild stimulant, causing the migration of macrophages which remove traces of silica present in the calcium dust. The harmlessness of calcium hydrate dust may be attributed both to its physical and to its chemical nature. When inoculation with tubercle bacilli follows a period of lime dust inhalation, there seems to be a very slight retardation in the development of tuberculous lesions which nevertheless are indistinguishable from the customary lesions of this infection in rabbits. When the lime dusting occurs after inoculation with tubercle bacilli, there is a more distinct retardation of the tuberculous development explainable on the ground that the lime causes an overproduction of macrophages which render inert the tubercle bacilli. As dissolved calcium is in the blood stream always as bicarbonate and phosphate, the excess, introduced by such experiments as have been detailed, must be deposited in those organs normally characterized by a high calcium content, such as the bones, kidneys, and lungs. In tuberculous condition where we have a calcium demineralization, any increase in calcium would tend to balance the existing deficiency and permit of an approach to normal.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 17, 1926

The Production of Conjugated Glycuronic Acids in Depancreatized Dogs.—A. J. Quick (from the Department of Physiological Chemistry, Medical School, University of Pennsylvania). Although glycuronic acid is chemically an oxidation product of glucose little is known concerning its relationship to carbohydrate metabolism. Normally it is produced in response to the presence of any one of a large group of aromatic compounds including benzoic acid, and borneol, a terpene alcohol closely related to camphor. The glycuronic acid combines with these substances and is excreted in the urine; and the conjugation is considered to be a detoxication mechanism. The precursor of glycuronic acid is not known, but its close structural relationship to glucose makes it appear probable that it is derived from carbohydrates. In order to obtain experimental data which might have a bearing on the possible connection of glycuronic acid to carbohydrate metabolism, the

production of conjugated glycuronic acid was studied in depancreatized dogs which presumably have lost the power to burn sugar. Following total pancreatectomy, the dogs were given insulin and kept on a meat and sugar diet until they had recovered from the effects of the operation. The dogs were then fasted and the insulin withdrawn. The sugar and nitrogen output were determined daily and when the D : N ratio had dropped to about 3, borneol, or benzoic acid, either of which is excreted largely as paired glycuronic in the normal dog, was administered. It was found that the amount of glycuronic acid produced was practically the same as for a normal dog, and, furthermore, that the excretion of glucose was markedly decreased following the ingestion of the drug. Since the nitrogen output remained practically unchanged, the D : N ratio showed an abrupt drop. If, however, the glycuronic acid calculated in terms of glucose, was added to the urinary glucose, and the D : N ratio calculated, a value was obtained which corresponded to the calculated ratio which would have been obtained for that day had no borneol or benzoic acid been fed. From these results it appears that glycuronic acid and glucose have the same precursor and that when there is a demand by the organism for the former the synthesis takes place at the expense of the potential glucose. Since the glucose produced in total diabetes during starvation is generally believed to be solely derived from protein, it can be concluded that the diabetic organism can still utilize that portion of the protein molecule which ordinarily goes to glucose, for the synthesis of glycuronic acid. The conjugated glycuronic acid of benzoic acid which heretofore had not been prepared was isolated in pure form. Its optical rotation is $[\alpha]_D^{20} = 25$. In alkaline solution it showed mutarotation. Its chemical properties indicate that the benzoic acid is linked in ester linkage to one of the hydroxyl group of the glycuronic acid, and, therefore, the compound should be named β.d. glycuronic acid monobenzoate.

The Influence of Cerebral Bloodflow on Respiration.—C. F. SCHMIDT (from the Laboratory of Pharmacology of the University of Pennsylvania). In the course of an investigation of the action of morphin and other drugs on the respiration of the cat, it was found (C. F. SCHMIDT, and W. B. HARER: *J. Exper. Med.*, 1923, **37**, 47) that a sharp change in blood pressure always affected respiration. The relation was usually in the direction of stimulation of breathing by a fall in pressure and depression by a rise, though if pressure had been low for some time a further fall often caused depression or failure of respiration, and a rise in pressure might stimulate breathing. An explanation of these events was suggested by an essay by R. G. PEARCE (*Arch. Int. Med.*, 1921, **27**, 139), who emphasized the dependence of CO_2 tension of arterial blood upon the rate of bloodflow through the respiratory center. We formulated it as the following hypothesis: The chemical regulation of respiration is effected by the concentration of stimulant material within the cells of the center, and this concentration depends on a balance among three factors: (1) The concentration in arterial blood; (2) the rate at which stimulant material is produced within the cells by their own metabolic activity; and (3) the rate of bloodflow through the center, which determines the extent to which metabolites can accumulate. Similar reasoning is evident in subse-

quent publications of H. WINTERSTEIN (*Pflug. Arch.*, 1921, **187**, 293) and R. GESELL (*Am. J. Physiol.*, 1923, **66**, 5). Winterstein attributes the hypernea of anoxemia to accumulation of lactic acid within the cells of the respiratory center because the supply of oxygen is inadequate for their metabolic needs—a "Centrogenous Hypernea;" he attempted to demonstrate an increased lactic-acid content of medullary tissues after anoxemia, but was unable to obtain conclusive results. Gesell has applied similar reasoning to the regulation of respiration under all conditions, not limiting it to anoxemia, and has stated a theory (*Am. J. Physiol.*, 1923, **66**, 5) that is identical with the hypothesis suggested to us by Pearce's paper. Gesell has adduced evidence from the literature that is in favor of this theory (*Physiol. Reviews*, 1925, **5**, 551), and MCGINTY, D. A. and GESELL, R. (*Am. J. Physiol.*, 1925, **75**, 70) have shown that lactic acid accumulates rapidly in cerebral tissues during anoxemia, but as their method involves complete interruption of bloodflow before analyses can be made, it is uncertain to what extent their results can be applied to physiological changes. It seemed to us that this hypothesis could be subjected to a physiological test by showing: (1) That activity of respiration always varies inversely as medullary bloodflow, and (2) that the gaseous metabolism of the medulla is always greater during hypernea of any cause than during quiet breathing. Both demonstrations involve actual measurement or control of bloodflow through the medulla or cerebrum, which has not been done by other investigators of the relation between bloodflow and respiration. We have devised methods for measuring cerebral or medullary flow, as total venous outflow or arterial inflow, and have perfused the cerebral arteries with blood by means of the Richards-Drinker pump (*J. Pharmacol. Exp. Therap.*, 1915, **7**, 467) in spontaeously breathing cats and dogs. Before investigating the relation between bloodflow and respiration, it was necessary to study the means by which cerebral flow could be altered, and this involved a study of the regulation of the cerebral circulation. We have found that: (1) Cerebral flow varies directly with systemic pressure, no matter how the latter is altered; (2) vasomotor nerves to cerebral vessels are of no functional significance, if they exist; (3) the cerebral arteries have an inherent regulation by virtue of constriction in response to increased alkalinity or oxygen tension, or cold, and of dilatation to increased acidity or CO_2 tension, heat, or decreased rate of flow, of blood reaching them. The vessels sometimes go into spasm, under circumstances that are not yet fully understood, though they include cold and probably excess alkali and oxygen. The respiratory responses to changes in medullary bloodflow are those demanded by the hypothesis, for respiration is augmented by a decrease in flow (within certain limits) and depressed by an increase in flow, no matter what means are used to alter flow. These have included hemorrhage, injection of blood or saline, exhibition of nitrites, adrenalin, and pituitrin, stimulation of vagus, splanchnic, and cervical sympathetic nerves, temporary occlusion of cerebral arteries, and alterations in perfusion flow. The effect is less marked, but of the same nature, when flow is changed during inhalation of CO_2 (5 to 75 per cent in oxygen) or of nitrogen. The metabolism of cerebral and medullary tissues is being investigated.

The Influence of Adrenalin on the Perfused Frog's Kidney.—A. N. Richards, J. B. Barnwell, and R. C. Bradley (from the Laboratory of Pharmacology, University of Pennsylvania). When blood was driven through the bloodvessels of the rabbit's kidney at constant rate per minute, it was found that the volume of urine eliminated from that kidney varied directly with changes in pressure within the renal vessels induced by vasoconstricting agencies, such as splanchnic nerve stimulation or injection of adrenalin (*Am. J. Physiol.*, 1922, **59**, 144). In such an experiment, when record was made of changes in size of the kidney during the constrictor action of adrenalin, it was found that the whole organ swelled. Thus, evidence was obtained that vasoconstriction and vasodilatation may occur simultaneously in this organ as the result of the action of adrenalin. It was conceived that this coincidence might be due to constriction of the efferent vessel from the glomerulus and that this impediment to outflow of blood from the glomerular capillaries was causing increased pressure in and passive distention of the glomerular capillaries. Evidence in support of this assumption was provided by the study of the influence of very minute doses of adrenalin and other renal vasoconstrictors in rabbits and in frogs (*Am. J. Physiol.*, 1922, **59**, 191; 1924, **71**, 178). It seemed desirable to perform experiments on the frog's kidney in which adrenalin should be tested under conditions insuring constancy of bloodflow through that organ, in order to learn by direct observation whether the glomerular tufts did actually swell when renal arterioles were constricted. A simple perfusion apparatus was designed and the results of the experiment recorded by photographs made at appropriate times during the course of the perfusion. The results show that adrenalin tested in whole frog's blood in concentration of 1 to 500,000 causes rise of perfusion pressure (constriction of vessels) and simultaneous increase in size of glomerular tufts. The conditions of the experiment were such as to make it almost certain that adrenalin in this concentration includes constriction of efferent vessels among its renal actions. The importance of the experiment consists in the demonstration that changes in caliber of the efferent vessel may occur as a result of physiological agencies, thereby justifying the conclusion that intraglomerular pressure and consequently intraglomerular urine formation may be regulated by alterations in the relative calibers of the afferent and efferent vessels. Physiologists have long thought that a regulation of this type existed, but directly supporting evidence has thus far been lacking.

Temperature Changes in the Tissues Accompanying Temperature Sensations.—H. C. Bazett and B. McGlone (from the Department of Physiology, University of Pennsylvania). Stimulation of warm and cold spots in the skin gives sensations referred to external objects, but less definite temperature sensations also occur associated with impressions of general body warmth. Spot stimulation is accompanied by after sensations, and may cause paradoxical sensations of the opposite temperature. It is not known whether both types of sensation depend on the same end organs, nor have these as yet been identified. Some data on the variations in the tissue temperature gradients accompanying general bodily sensations have been already published in abstract (*Am. J. Physiol.*, 1926, **76**, 224),

and attention is here directed to the problem of skin stimulation. Thermocouples consisting of steel needle tubing (0.35 mm. diameter) and with a constantan core have been employed, at depths determined by Roentgen ray. Observations have also been made using loops of wire 0.06 mm. diameter introduced by a sewing needle. For point stimulation a von Frey esthesiometer has been brought in contact with the skin using a ratchet, giving very light contact. When a point stimulus (1.5 mm. diameter at 20° C.) is applied to the skin for a few seconds, the surface temperature falls immediately and rapidly and on removal of the stimulus it rises rapidly at first, then more slowly. The initial temperature is not regained for several minutes. At depths of 9 mm. (in the subcutaneous tissue) the recordable changes rarely exceed 0.05° C., and may not commence for ten seconds or more, so that the maximum change may occur 0.5 minute after removal of the stimulus. Warm stimuli give similar but reverse changes both on the surface and at considerable depths. Complicated changes of considerable size and less delayed occur at some 2 or 3 mm. depth; a cold stimulus may give an initial slight rise of temperature followed by a considerable fall which in turn may show two steps, an earlier step and a later slower change, the latter often occurring after removal of the stimulus. In consequence, the lowest temperature may be reached long after such removal. With warm stimuli there may be similarly an initial parodoxical fall, but the later rise usually has no steps. If, however, the stimulus applied has a temperature of about 40° C. or higher, a steplike rise is often seen accompanied by a hot rather than a warm sensation. At depths of about 1 mm. the curves become simpler resembling more closely those obtained from the surface. There is evidence, therefore, of conduction of heat slowly, probably along the bloodvessels with accompanying vasomotor reaction. The sensations appear to be derived from the superficial layers, since warm sensations appear simultaneously with temperature changes at approximately 1 mm. depth; the end organs for cold are apparently more superficial, since in every case the sensation has been recorded before temperature changes at the depths investigated. The changes occurring at depths less than 1 mm. are now being investigated. Our thanks are due to the Ella Sachs Plotz Foundation for a grant toward the expenses of this research.

Crenation of Human Red Blood Corpuscles in Microscopic Preparations.—B. McGlone (from the Department of Physiology, University of Pennsylvania). This phenomenon is usually ascribed to an osmotic process due to increasing concentration of the suspending medium by evaporation at the margin of the preparation. Brinkman and van Dam (*Biochem. Zeitschr.*, 1920, **108**, 52) suggested that crenation is due to a charge on the microscopic slide produced by friction of the linen employed for drying. In the experiments here reported crenation has been observed on those microscopic preparations in which clean microscopic slides and cover glasses were rubbed with clean silk, cotton or linen cloths, and when there was no evident evaporation. With silk and cotton the charge is positive, with linen negative as evidenced by a gold leaf electroscope. In suspensions of human red blood corpuscles in 0.9 per cent NaCl solutions, within two to five seconds after adjusting

the cover glass crenation occurs in those cells close to the cover glass and possibly in moving contact with it, followed ten seconds later by crenation on the surface of the slide as the cells settle. The margin of the cell becomes irregular, then the surfaces of the disk wrinkle, and the cell wall puckers. These processes, coarse initially, become fine, conical and filamentous, and the body of the cell assumes a spheroidal form within one to two minutes, although occasionally the end result is delayed. Protected against evaporation, these preparations persist; apparently crenation is not a stage in the formation of uniform spheroidal forms. Occurring most readily in isotonic NaCl solutions with about a 1 per cent cell suspension and a plasma content of 5 per cent or less, nevertheless crenation is observed in concentrations of NaCl from 2.9 per cent to 0.37 per cent, in solutions hypertonic and hypotonic. In higher concentrations than 2.9 per cent the deformation is confined to a curling or wrinkling of the margin of the cell. In NaCl solutions adjusted for varying hydrogen-ion concentrations, crenation occurs over a wide range, from pH 4.7 to pH 8 approximately. Apparently, the greater the cell suspension the more complete and more rapid the crenation. The phenomenon also takes place on charged quartz. Substituting as suspending media balanced salt, 10 per cent sucrose or isotonic $CaCl_2$ solutions does not alter the result. Crenation is not observed in preparations on glassware which is: (1) Not charged; (2) decharged by flaming; (3) charged but coated with a thin film of paraffin oil. Serum is protective; crenation does not appear in preparations where the suspending NaCl solution contains 30 per cent or more serum, but is complete when serum content is 5 per cent or less. The addition of a trivalent ion Al^{+++} to the suspending solution in dilute amounts varying with the cell suspension prevents crenation. In part the observations of the authors cited and those of GOUGH (*Biochem. J.*, 1924, **18**, 202) and of MILLAR (*Quart. J. Exper. Physiol.*, 1925, **15**, 253) are confirmed.

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